SARCOMAS REVISITED

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by

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DECLARATION

I, DERYCK ARNOLD TAYLOR, hereby declare that the work on which this thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other University.

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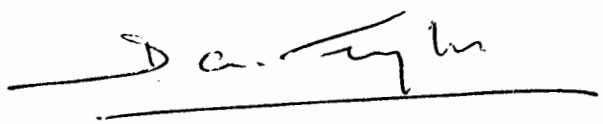

31st January 1992

intercontinental mezzoforte exhortatory contact which supplemented the more mezzopiano one of

Dr Helen Wainwright. Her watchful and knowledgeable eye at the `hot seat' provided a most vivid and rewarding experience of diagnostic pathology.

My fellow Registrars, from whom I learned much on a casual daily basis.

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ACRONYMS

Use of acronyms for sarcomas has been made:

1. in tables and diagrams where necessitated by lack of space, although this has been minimised in Figs. 5 to make them as self-contained as possible.
2. in text sections where the unabbreviated form has already been established within the sections.

AAT	Alpha-1-antitrypsin
ASPS	Alveolar Soft Part Sarcoma
CCS	Clear Cell Sarcoma
DFP	Dermatofibrosarcoma Protuberans
EGCT	Extraskeletal Giant Cell Tumour
EM	Electron Microscopy
EMA	Epithelial Membrane Antigen
GFAP	Glial Fibrillary Acidic Protein
IHC	Immunohisto-chemistry/chemical
MFH	Malignant Fibrous Histiocytoma
MGranCT	Malignant Granular Cell Tumour
MHE	Malignant Haemangioendothelioma
MHP	Malignant Haemangiopericytoma
MM	Malignant Mesenchymoma
MPNST	Malignant Peripheral Nerve Sheath Tumour
MSA	Muscle-Specific Actin
NOS	Not Otherwise Specified

NSE	Neuron-Specific Enolase
SNOMed	Systematised Nomenclature of Medicine
SNOP	Systematised Nomenclature of Pathology
SS	Synovial Sarcoma
US	Ultra-structure/structural

(The suffix -sarcoma has generally been omitted from tables except where the tables contain references to benign tumours).

CHAPTER 1
INTRODUCTION

The diagnosis by light microscopy of the malignant tumours of soft tissues known as sarcomas has always been difficult and a touchstone of histological acumen.[1,2,3,4] This has been exacerbated by confusions in nomenclature, and debate concerning what is, and what is not, a sarcoma when considering low-grade lesions.[5] Another dimension is added to the problem when, as happens not infrequently, an undoubted sarcoma is poorly-differentiated,[6] or shows `dedifferentiation'[7] (a term used to describe anaplastic components resembling MFH in sarcomas of another type such as liposarcoma). Yet another considerations are added by the importance of grading,[8] and staging.[9,10]

Treatment modalities can depend very heavily on the diagnoses rendered, which are therefore crucial to patient welfare. This gives the field a fascination increased by the comparative uncommonness with which the entities are encountered. This infrequency means that expertise in the field is not to be acquired from the occasional sarcomas encountered amongst daily routine specimens from general surgery.

In the last decade, the technique of IHC has become available. In ideal cases, this enables the pathologist to show the direction in which the cells of a tumour are attempting to evolve. This can permit a specific diagnosis of

sarcoma type when morphological differentiation is so poor that the only diagnosis renderable with accuracy and truth would otherwise be "Sarcoma (NOS)".[11] The advent of this technique has somewhat displaced EM without eliminating it - in the difficult field of sarcoma diagnosis, nothing of potential assistance is ignored.

The diagnostic categories of sarcoma have also been constantly refined, with quantum leaps in rationalisation brought about by the advent of the newer methods just mentioned. The process continues with the discovery and expansion of tumour-specific translocations[12] such as t(X;18], t(12;160 and t(11;22) in synovial sarcoma, myxoid liposarcoma and malignant peripheral nerve tumours. One of the present consequences is that categories of tumour once commonly invoked (for example, fibrosarcoma) are now hardly ever diagnosed.

The scope of this study has four aspects, the third and fourth of which are intended to give the dissertation practical value as a sourcebook and basic guide to the diagnosis of sarcomas.

1. Reassessment of Historical Material.

Sarcomas diagnosed in the Department of Pathology in the years 1960-4 are re-examined. This is long enough ago for a definite disadvantage to exist in terms of techniques then available, but recent enough for diagnostic categories (by pure

morphological criteria) to be essentially recognisable and mostly consonant with those in current use. These cases have been re-examined by light microscopy (Chapter 5). Where a discordant diagnosis thereby resulted, the case was submitted to IHC (assuming blocked tissue was still available, which was not always the case) in an attempt to resolve or refine the matter. EM as a diagnostic modality was not used, because it would have involved the destruction of irreplaceable tissue blocks for doubtful advantage. There has been no attempt to secure clinical input to determine the lethal potential of tumours; follow-up will have been variable and the issue is not whether the original diagnosis was "right" - it is whether a contemporary pathologist faced with the same material as his historic counterpart would reach the same conclusion. It has to be emphasised very clearly that in this intriguing and challenging area of tumour diagnosis, many cases are still (and perhaps always will be) a matter of opinion. Were it otherwise, the field would not hold the interest it does.

2. Current Incidence.

An analysis has been made of the records of all tumours diagnosed as sarcomas from computerised systematised nomenclature records for the years 1986-90, for comparison with the earlier five-year period. Then, because the numbers were felt to be rather small and perhaps misleading for the rarer sarcomas, and because microfiched systematised nomenclature records were available for cases from 1971-82

(with the exception of 1979), representing a middle period, these too were collected as a third, much larger, group. No attempt was made to review slides more recent than 1964. The most recent material is axiomatically reliable, being made by a variety of pathologists from a contemporary perspective and with full contemporary advantages, and a review of the middle period slides would have been a mammoth undertaking, beyond the scope of this dissertation.

A comparison is made between the incidences of sarcoma type as diagnosed in Groote Schuur Hospital in the 5-year period 1960-4, before and after revision; in the 5-year period 1986-90; and in the 11-year period 1971-82 (omitting 1979), with comments on the discrepancies (Chapter 3). Findings are compared with those of other series (Chapter 4).

3. Diagnostic Synopsis.

An attempt is made to consolidate the morphological criteria used in the diagnosis of sarcomas as a series of Venn diagrams of the diagnostic categories, showing how cell characteristics, architectural patterns and stromal types, can combinatively lead to a differential - or at best, unique - diagnosis (Chapter 6).

4. Literature Update.

The sarcoma literature in the major journals has been surveyed since the publication in 1988 of the second edition of Soft Tissue Tumors,[13a] and updated references are given for each sarcoma type where described in Chapter 5.

CHAPTER 2
MATERIALS & METHODS

All cases with the morphological coding of `sarcoma' fell into the ambit of the study. Initially, it was felt that this should follow the precedent set by, and include all tumours covered in Soft Tissue Tumours.[13a] This would have resulted in the retention of some rather disparate entities whose status as sarcomas is arguable. Examples are malignant paraganglioma, chordoma, and neuro-blastoma and -epithelioma. However, no such cases were retrieved in sufficient numbers to justify their inclusion, so that in practice, the tumours (and SNOMed morphology codes) covered by this study are:

Sarcoma Not Otherwise Specified (88003)

Spindle Sarcoma (88013)

Epithelioid Sarcoma (88043)

Malignant Fibrous Histiocytoma (88303) (including Fibroxanthoma (88313))

Dermatofibrosarcoma protuberans (88323)

Fibrosarcoma (88103)

Myxosarcoma (88403)

Liposarcoma (88503)

Leiomyosarcoma (88903)

Rhabdomyosarcoma (89003)

Malignant Mesenchymoma (89903)

Synovial Sarcoma (90403)

Clear Cell Sarcoma (90443)

Angiosarcoma (91203)

Malignant Haemangioendothelioma (91303)

Kaposi's Sarcoma (91403)

Malignant Haemangiopericytoma (91503)

Extraskeletal Osteosarcoma (91803, Extraskeletal)

Extraskeletal Chondrosarcoma (92203, Extraskeletal)

Extraskeletal Giant Cell Tumour (92503)

Ewing's Sarcoma (92603)

Malignant Peripheral Nerve Sheath Tumour
(comprising Neurofibrosarcoma (95403) and
Malignant Schwannoma (95603))

Malignant Granular Cell Tumour (95803)

Alveolar Soft Part Sarcoma (95813)

(These are classified in order of increasing SNOMed Morphology code, and this is the order maintained in subsequent survey discussions and tables. Mesotheliomas have been ignored for topographical reasons - the exclusive definition of `Soft Tissue' used in selecting cases is given below).

It was sometimes difficult to decide what diagnosis was in fact originally rendered. Reports on sarcoma sections tend by their very nature to be discursive and contain a list of differential diagnoses considered. Of great assistance was the SNOMed or SNOP codes actually assigned by the pathologist, and in cases of ambiguity of the report, these were generally accepted as definitive, except where in conflict with an obviously carefully-considered report. Such discrepancy sometimes occurred because proper use of the Systematised

Nomenclature coding had not been made - advantage is regrettably not invariably taken of codes permitting distinction, on an ascending scale of specificity, between

possible malignancy,

definite malignancy not necessarily mesenchymal,

Sarcoma NOS (i.e. definite mesenchymal malignancy),

Sarcoma Spindled/Giant cell/Small cell/Epithelioid, and

Sarcoma (Specific Subtype).

(However, these were not in any case available for material prior to 1971).

A NEED IS HIGHLIGHTED for reports to give specifically, in words, the morphological and topographical assignments intended, to counter the possibility of infrequent but annoying lack of clarity. Reports on sarcomas, because of their complexity, are not infrequently discursive and descriptional, and this can lead to unintentional discrepancies within the same report, and more frequently to discrepancy between different reports on the same tumour submitted for examination at different times. Where doubts existed as to whether a diagnosis was speculative or favoured, the diagnosis allocated for this study was the one which seemed to reflect the report most accurately. This requires a qualification: in many cases, one diagnosis was favoured above others which were not excluded. In such circumstances, the favoured diagnosis is recorded as absolute, but in the compilation of cases given in the Appendix, this fact is indicated by a question mark against the case.

`Soft Tissue' as a topographical site is strictly defined as non-visceral. Though some interesting cases are thereby lost, tumours of the genitourinary tract are excluded (apart from those of the vagina and distally), as are tumours of the gastrointestinal tract (apart from those of the pharynx and proximally). Of mesenchymal malignancies, those in breast and central nervous system (including eye) were excluded because of their peculiarities which qualify them as studies in themselves. The thoracic, abdominal and pelvic cavities presented interpretational difficulties. Tumours within them are generally not included unless clinically noted to involve the chest wall or retroperitoneum. However, clinical descriptions usually left much to be desired, and here too, decisions were made that were of necessity arbitrary at times. Metastatic specimens are not included in the statistics, although the reference number quoted where more than one specimen from the same patient were separately submitted is sometimes that of a late or metastatic specimen because the material is histologically better or the report more definitive. An attempt was made to quote the latest report of a particular case falling in the periods surveyed, and ensure that it contained a reference to the previous reports, where such were known to exist. Patient names were checked to exclude multiple entry. It was found that reports generally but not invariably gave reference to extant previous histology, and in a very small number of cases, it was

interesting to find a later divergent report made in apparent ignorance of an earlier one.

Cases referred from hospitals outside those served by the University Department of Anatomical Pathology are excluded, unless the material was referred along with the patient, as frequently happens when radiotherapy is undertaken. Such cases were identified by the the presence of a request accompanying referred tissue/slides that the report be sent to a ward in Groote Schuur Hospital. A possible inconsistency in numbers may result from the unknown number of "outside" patients diagnosed by this Department on referred material as having sarcoma in advance of subsequent admission to Groote Schuur Hospital for treatment.

Case records for the period 1960-4 were searched seriatim for those meeting the above criteria. For the period 1971-82, records were searched via the microfiche for morphology codes appropriate to the topographical and other selection criteria defined above (1979 being excluded because the relevant microfiche is not available). For the period 1986-90, computerised records were accessed, cases with the appropriate morphology codes printed out and those with inappropriate topography excluded. In every surviving case the original report was then checked before being admitted to this study.

Slides for the cases obtained from the 1960-4 records were drawn from the archives and reassessed on purely morphological grounds. In some cases, restaining or resectioning from the block was necessary. Those cases in which it was felt that the

original diagnosis could be safely amended without further investigation (generally `fibrosarcomas' now classifiable as MFH) were taken no further. Those in which IHC or other special stains were felt to offer the hope of confirming original and/or current tentative diagnosis or resolving an ambiguity were submitted to such further investigation. In this, some cases presented an impasse: blocks were missing or cut away, or seemed not to correspond to the description given at the time. This highlights another practical recommendation, namely that the number of blocks of tissue taken should be routinely recorded in all reports for archival purposes, to obviate perhaps vital blocks going unknowingly missing.

The IHC methods used were those standard for the commercial antibodies. No modifications are known, or were made, to accomodate the age of the material. As there is no way to determine time of formalin fixation of the original tissue, it is quite possible that a number of IHC failures may be due to hyper-fixation.

CHAPTER 3
SARCOMAS THEN & NOW

Table 1 shows the distribution of sarcoma diagnosis among the diagnostic categories for the three periods under consideration, together with the amended distribution for the earliest. (Comments on the way in which these amendments were made, and the way in which they illustrate the pitfalls and dilemmas of diagnosis of sarcomas as a group, are the subject of Chapter 5).

The numerical comparisons are merely to be taken as suggestive, since apart from the first group, no attempt has been made at standardisation by review of the slides, and the diagnoses have been made by many different pathologists, with almost certainly differing criteria. Criteria will also have altered over the periods considered because of refinements in understanding and the description of new entities. Indeed, it is the argument of this dissertation that disparity between the groups is to be expected, the intention being to draw conclusions from them where possible.

Total numbers of all cases received for histology by the Department of Anatomical Pathology of the University of Cape Town were 52 351 for the period 1960-4, 160 939 between 1971-82 (omitting 1979), and 90 672 between 1986-90, and for purposes of comparison between each period, the numbers of cases given in Table 1 have been normalised () to incidence per 100 000 specimens (of all kinds) submitted for histology

TABLE 1

DIAGNOSTIC INCIDENCE OF SARCOMA BY TYPE

(in order of SNOMed listing)

number of cases and

(number per 100 000 specimens to nearest integer)

TYPE	1960-4	1960-4 reinterpreted	1971-82 (1979 omitted)	1986-90
Sarcoma NOS	32 (61)	3 (6)	48 (30)	25 (28)
Epithelioid		1 (2)	4 (2)	1 (1)
Fibro-	11 (21)	3 (6)	22 (14)	1 (1)
MFH*		14 (27)	28 (17)	29 (32)
DFP*	4 (8)	8 (15)	14 (9)	11 (12)
Myxo-	2 (4)	0	0	0
Lipo-	5 (10)	3 (6)	53 (33)	7 (8)
Leiomyo-	4 (8)	6 (11)	8 (5)	9 (10)
Rhabdomyo-	4 (8)	4 (8)	27 (17)	12 (13)
MM*	1 (2)	0	1 (1)	1 (1)
SS*	2 (4)	5 (10)	17 (11)	12 (13)
CCS*		1 (2)	6 (14)	2 (2)
Angio-	0	0	4 (2)	4 (4)
MHE*	0	2 (4)	1 (1)	0
Kaposi's	3 (6)	2 (4)	29 (18)	20 (22)
MHP*	2 (4)	2 (4)	2 (1)	1 (1)
Osteo^{E}-	0	0	0	2 (2)
Chondro^{E}-	0	0	1 (1)	1 (1)
EGCT*	0	1 (2)	3 (2)	0 (0)
Ewing's^{E}	0	2 (4)	0	4 (4)
MPNST*	6 (11)	7 (13)	18 (11)	11 (12)
MGranCT*	0	0	0	1 (1)
ASPS*	2 (4)	3 (6)	3 (2)	0
TOTAL	78 (149)	67 (128)	289 (180)	154 (169)

* Acronyms - see p v

E - Extraskeletal

in each. Additionally, the data resulting from current reinterpretation of the 1960-4 cases is shown in bold figures. (All manipulated figures are rounded off to integers).

I ALL SARCOMAS

The total incidence of sarcomas in submitted material has increased markedly in the last 30 years (the 128 cases per 100 000 - as reassessed - of thirty years ago growing to 169 today), but appears to have reached a plateau. Some caution is needed in interpreting the figures, since it could be argued that the pattern of <u>all</u> histology submissions has altered: sarcomas may not have increased - their dilution by `other' specimens may simply have decreased. A separate study would be required to establish this point, but given the modern tendency to meticulously submit surgical specimens for, among other reasons, litigative security, and the massively increased numbers of gynaecological and skin biopsies, dilution of sarcomas is more likely to have increased than the reverse, and it seems at least possible that sarcoma specimens are truly more commonly encountered than they used to be. The reason also does not appear to be that they were underdiagnosed thirty years ago, since a reappraisal of the material resulted in 11 of 78 specimens (14 %) being reallocated a diagnosis other than soft tissue sarcoma. The converse parameter - the number of sarcoma diagnoses missed - is unknown.

If the proportion of sarcoma specimens has truly increased, is this because sarcomas now occur more frequently than they did? It seems inherently unlikely, although within the group, it is difficult to account for the tremendous incidence of liposarcoma specimens in the middle period of the three surveyed purely by changes in investigational and management procedures. It seems likely, though, that two factors may have resulted in the apparent increase of sarcomas as a whole. One is that more tumours are submitted because of the availability of needle biopsy (paradoxically, of very limited value in this area of oncology). The other is the rise of radiotherapy and the expert in soft tissue pathology, both of which have resulted in cases being increasingly referred to this hospital.

Table 2, using the data of Table 1, shows, for each period, the approximate percentage (relative to all sarcomas diagnosed in the period) of each morphological category (the figures have been rounded to the nearest integer so that the sums are not exactly 100). Table 3 groups the findings into three: common, uncommon and rare sarcomas.

The distribution of diagnoses for all periods combined is shown histogrammatically in Fig. 1. Fig. 2 shows just the most recent series (1986-90) for comparative purposes, listed in the same order as in Fig. 1. Figs 3 and 4 show the effect of reinterpretation on the two largest original subgroups of sarcoma: sarcoma NOS and fibrosarcoma, respectively.

TABLE 2

ASSIGNED MORPHOLOGY AS % OF ALL SARCOMA MORPHOLOGY

TYPE	1960-4	**1960-4 reinterpreted**	1971-82 (1979 omitted)	1986-90
Sarcoma NOS	41	**4**	17	16
Epithelioid		**1**	1	<1
Fibro-	14	**4**	8	<1
MFH*		**21**	10	19
DFP*	5	**12**	5	7
Myxo-	3	**0**	0	0
Lipo-	6	**4**	18	5
Leiomyo-	5	**9**	3	6
Rhabdo-	5	**6**	9	8
MM*	1	**0**	<1	<1
SS*	3	**7**	6	8
CCS*		**1**	2	1
Angio-	0	**0**	1	3
MHE*	0	**3**	<1	0
Kaposi's	4	**3**	10	13
MHP*	3	**3**	<1	<1
Osteo-E	0	**0**	0	1
Chondro-E	0	**0**	<1	<1
EGCT*	0	**1**	1	0
Ewing's E	0	**3**	0	3
MPNST*	8	**10**	6	7
MGranCT	0	**0**	0	<1
ASPS*	3	**4**	1	0

* Acronyms - see p v

E - Extraskeletal

Figures are rounded to the nearest integer

TABLE 3

QUALITATIVE RANKING OF DIAGNOSTIC FREQUENCY WITHIN SARCOMAS

(The findings are the same for each of the 3 periods except where otherwise specified).

COMMON (generally >10%)

Sarcoma NOS[1] (uncommon 1961-4 reinterpreted), MFH[2*], Kaposi's[3] (rare 1961-4 before/after reinterpretation)

UNCOMMON (generally 5 - 10%)

DFP* (common 1961-4 reinterpreted), Lipo- (common, 1971-82), Leiomyo- (rare, 1971-82), Rhabdomyo-, SS* (rare, 1961-4 before reinterpretation), MPNST*

RARE (generally <5%)

Epithelioid, Fibro-[4] (common, 1961-4 before reinterpretation), Myxo-, MM*, CCS*, Angio-, MHE*, MHP*, Osteo-[E], Chondro-[E], EGCT*, Ewing's, MGranCT*, ASPS

* Acronyms - see p v

1 - marked decrease overall

2 - less frequently diagnosed in the 1971-82 period

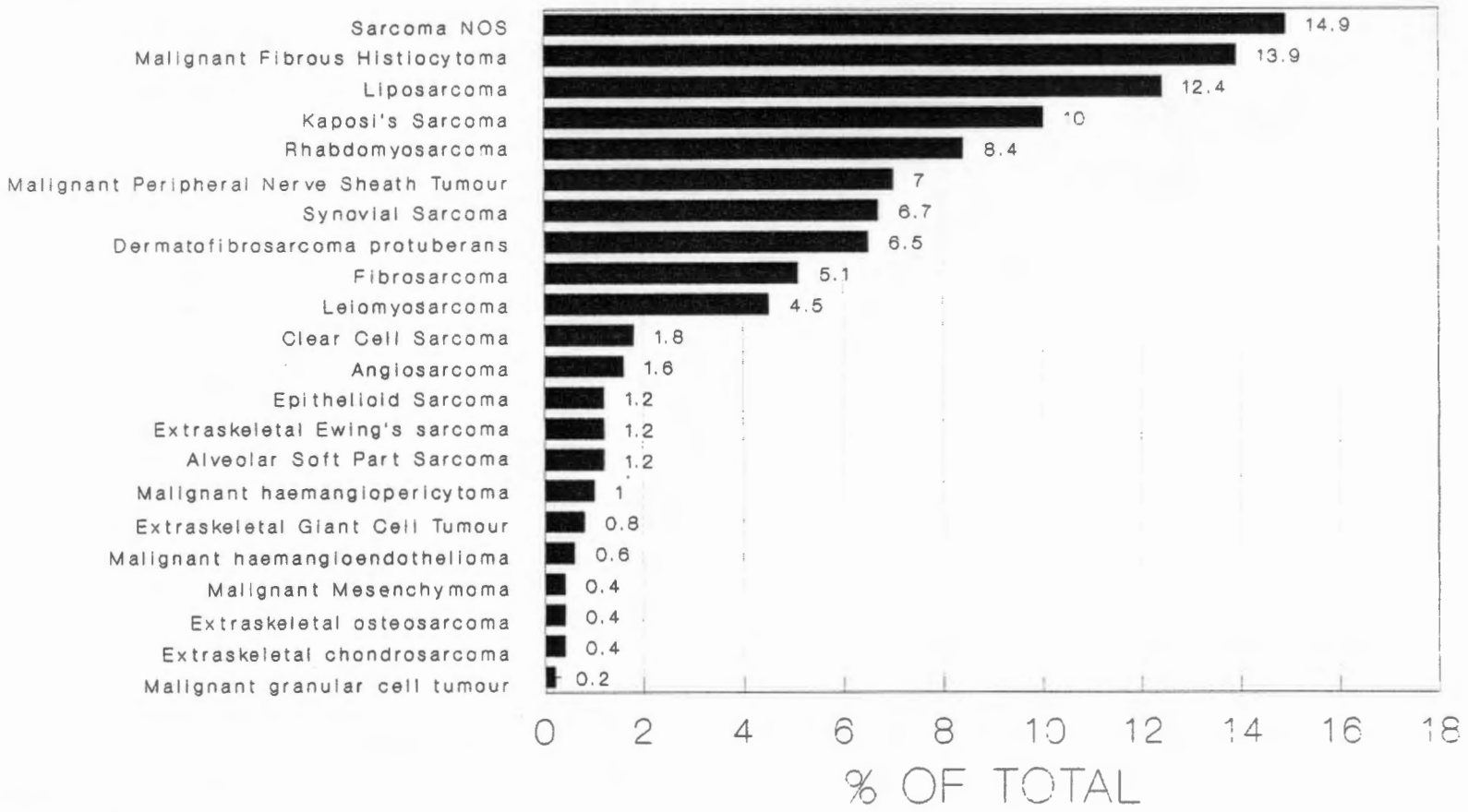
3 - marked steady increase in diagnosis and now common.

4 - marked decrease in diagnosis and now rare.

E - Extraskeletal

Fig 1 **Distribution of Sarcoma Types**

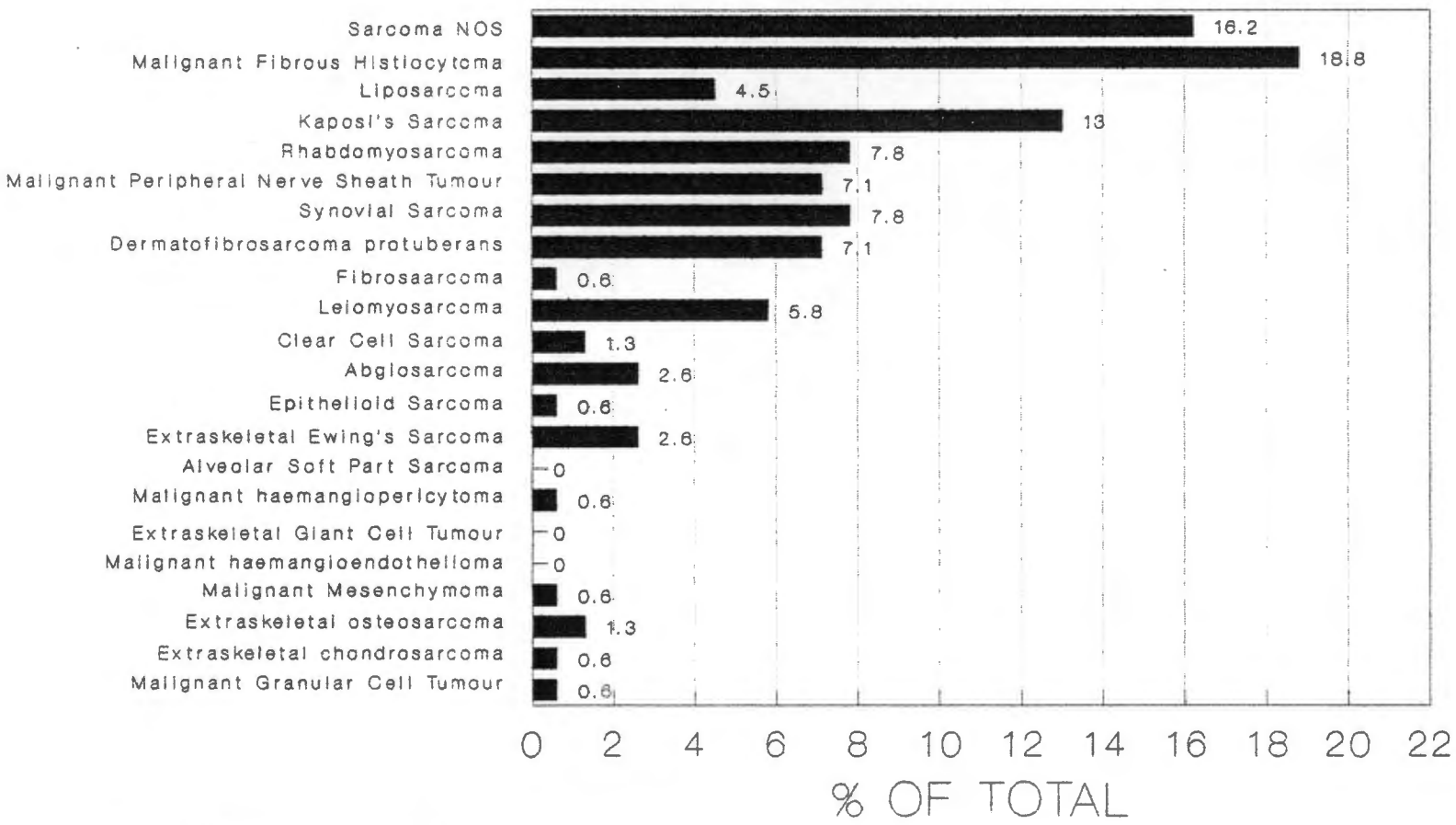
early (reinterpreted)/middle/late series combined*



*510 cases, selection criteria as discussed in Chapter 2

Fig 2 **Distribution of Sarcoma Types**

late series (1986-90)*



*154 cases, selection criteria as discussed in Chapter 2 (shown in the same sequence as for combined series)

II SARCOMAS BY TYPE

The most striking finding, considering the data in Table 2, has been the decrease in the diagnosis of Sarcoma NOS and Fibrosarcoma over the years. Sarcoma NOS has shrunk, it is generally argued, because of the advent of IHC and US techniques. In 1960-4, 32 of 78 sarcomas (41%) were not further diagnosable; by applying IHC and modern diagnostic categories, this was reduced to 3 of 67 (4%) (and in 2 of these, a diagnosis might still have been possible if blocks had been available for IHC); 10 of the originals were felt not to be sarcomas, and one not to be a soft tissue sarcoma. Yet the rationalisation is less due to modern techniques than to a clearer understanding of sarcomas and an expansion of the diagnostic categories largely by morphological criteria! This argument is supported by the fact that as few sarcomas were diagnosed as `not otherwise specifiable' in the middle period cases of 1971-82, before IHC became available as they were after. In fact, it is rather striking that the figures for this period (48 of 289 diagnoses, 17%) is no different from those of the late period cases of 1986-90 (25 of 154 cases, 16%)!

The single most important category in rationalising sarcoma diagnosis has been that of MFH.[14] Many of the cases previously diagnosed as `sarcoma NOS' or `fibrosarcoma' fell into the new category, and it was principally for this reason, rather than the advent of IHC, that unspecifiable sarcoma and fibrosarcoma diminished in diagnostic frequency. In fact, the

diagnosis of MFH is in danger of becoming a net, as fibrosarcoma and unspecifiable sarcoma used to be. Attention has been drawn by Dehner[15] to the `nosologic haven' provided by MFH for difficult-to-classify, pleomorphic sarcomas. The pattern of MFH may be arranged like MPNST, sclerosing liposarcoma, fibrosarcoma and haemangiopericytoma, or disarranged like pleomorphic lipo- or rhabdomyo-sarcoma or leiomyosarcoma (see Chapter 5). It accounts for a fifth of all cases, in the early (revised) and late groups, but for only a tenth in the middle group, perhaps because of the contribution made by liposarcomas.

From Tables 2 & 3, it will be seen that there is substantial concurrence between periods on most entities Those for which agreement is lacking are:

Sarcoma NOS and fibrosarcoma, for reasons already explained.

DFP over-represented in the reinterpreted earliest group,

Liposarcoma, over-represented in the 1971-82 group

Leiomyosarcoma under-represented in the 1971-82 group.

Kaposi's sarcoma, showing an increase with time.

The frequency variations in MHP and leiomyosarcoma may be more apparent than real (especially in the case of the former) since the numbers are small, and it is not proposed to discuss the matter further.

1. Liposarcoma vs other myxoid sarcomas.

One speculates that perhaps a number of pleomorphic liposarcomas in the middle group could be recategorised as myxoid MFH, thereby adjusting the balance between both groups to something more like that seen in 1986-90. Myxoid rhabdomyosarcoma and MPNST might also, on reinvestigation, prove to increase at the expense of liposarcoma. In view of the fact that the diagnosis of liposarcoma was almost invariably made with confidence, it is unlikely that lipomas/myxomas accounted for many cases. If a `lacy' pattern is present, sarcomas other than liposarcoma are unlikely (Chapter 5), the only ones warranting consideration being epithelioid leiomyosarcoma, clear cell sarcoma and myxoid (botryoid) rhabdomyosarcoma, which are rare. The only liposarcoma with an `arranged' pattern is the sclerosing liposarcoma, which is the least common liposarcoma, so that the wide number of differential diagnoses it raises can be ignored as a source of potential significant misattribution in our data. Liposarcoma with a `disarranged' pattern is essentially pleomorphic liposarcoma, and this can mimic MFH and rhabdomyosarcoma, as already mentioned, but in the middle period, only one liposarcoma in 7 was reported as pleomorphic, the remaining 6 being almost equally divided between myxoid and well-differentiated. One is left with the conclusion that the middle period liposarcomas warrant reappraisal.

2. Leiomyosarcoma vs MFH, monophasic SS, MPNT, embryonal rhabdo-myosarcoma.

Considering the relatively underdiagnosed leiomysarcomas of the middle period, a number of differentials exist for the `sweeping' pattern (see Chapter 6). The `sweeping' pattern classically characterises leiomyosarcomata, although they can on rare occasion have an `arranged' pattern when palisades are present, or less uncommonly, a `disarranged' pattern when architecturally more anarchic (Chapter 6).

First, discussing only differentials for the `sweeping' pattern, fibrosarcoma and haemangiopericytoma can be discounted as potential sources of `extra' leiomyosarcomas because of their rarity, leaving monophasic SS, MPNST and rhabdomyosarcoma. None of these were apparently relatively over-diagnosed during the period, so are, purely on numerical grounds, an unlikely source of additional cases. However, they can present diagnostic pitfalls, making distinction dependent on minor features. Thus, whilst giant cells, necrosis and vascular stroma may be a feature of MFH and leiomyosarcoma alike, inflammatory cells are not usually found in leiomyosarcoma, and hyaline stroma is not usually found in MFH; whilst monophasic epithelioid SS and MPNST may, like leiomyosarcoma, have myxoid, vascular or hyaline stroma, inflammatory cells may be present in SS, and the cells of MPNST are characteristically wavy; whilst myxoid and vascular stroma may be a feature of both leiomyosarcoma and rhabdomyosarcoma, hyaline stroma is not found in the latter.

Turning to the `disarranged' leiomyosarcoma, this has already been mentioned (in consideration of the possible overdiagnosis of liposarcoma) as a differential of the pleomorphic liposarcoma, of which there were 6 diagnosed in the middle period. Although both leiomyo- and pleomorphic lipo-sarcoma may exhibit a myxoid or a fibrillary stroma, the hyaline stroma, if found, should permit a distinction in favour of leiomyosarcoma.

In the reassessment of 1960-4 cases, 2 out of 32 cases described as `Sarcoma NOS' were reallocated to leiomyosarcoma, so that the category of unspecified sarcomas would not seem a good source of leiomyosarcomas. Yet this is the likeliest explanation for the under-representation of leiomyosarcomas in the middle period. Of the 289 1971-82 sarcomas, 48 were diagnosed as `Sarcoma NOS', representing 17%, and 8 were diagnosed as `leiomyosarcoma' representing 3%. If a mere 10% of `sarcoma NOS' proved on reassessment to be leiomyosarcomata, which is quite possible, then the percentages of `sarcoma NOS' and leiomyosarcoma diagoses for the period would become 14 and 6% respectively, which would not differ greatly from the 1986-90 figures. This would illustrate the diagnostic difficulty provided by plump spindle-celled malignancies when IHC and EM are unavailable to take the diagnosis further, resulting in the safest diagnosis being one of uncategorised sarcoma.

3. Kaposi's Sarcoma

The recent increase in clinical cases is attributed to the association with HIV infection[16] and iatrogenic immunosuppression, although AIDS- and transplantation-related Kaposi's sarcoma are only two of four forms of the disease. The others are chronic, and lymphadenopathic[13b] (which roughly correspond to the epidemiological types sporadic and endemic.[17] However, the statistics of Table 2 show that the rise in histological cases antedated the AIDS epidemic which began after the middle period surveyed.

Although there is growing familiarity with the entity, the diagnostic criteria have not changed. Two of the three diagnoses made on the earliest material were confirmed on review (the third was thought to be a malignant haemangioendothelioma), and no additional cases found among the other sarcomas. However, it is not possible to say how many Kaposi's sarcomas might have been misdiagnosed as benign neoplasms such as haemangioma, or as non-neoplastic lesions such as pyogenic granuloma and fasciitis, which enter the differential.

Kaposi's sarcoma is characterised by a `sweeping' pattern without the hyaline stroma (Chapter 6) which can help distinguish leiomyosarcoma, MPNST and monophasic synovial sarcoma. Because of its vascularity, it needs to be differentiated from angiosarcoma, haemangioendothelioma and haemangiopericytoma, which are rarer. The cells of Kaposi's sarcoma (thought to be of vascular endothelial origin)[18] lack

the epithelioid appearance of these, though the distinction can be difficult. Embryonal rhabdomyosarcoma and biphasic synovial sarcoma are commoner and also may be vascular, but the distinction is not generally a problem.

If the local increase in Kaposi's sarcoma in the 1970s is real, could HIV have been responsible long before it was identified in the Northern Hemisphere? If that were the case, why was the prevalence of HIV seropositivity so low when testing for it began in South Africa in the mid-1980s? The dramatic increase in seropositivity has only been recent. May the 1970s increase rather be suggestive of an aetiological factor additional to those currently recognised? It is interesting to note that an increase in Kaposi's sarcoma similar to the one suggested by the data of Table 2 has been documented in Sweden, occurring in the elderly at the end of the 1960s, when Kaposi's sarcoma doubled. This has been adduced as possible evidence for the role of a hitherto-undetected retrovirus.[19] The aetiology of Kaposi's sarcoma is not clearly defined; a number of viruses including HIV and CMV, and even a dual viral infection with CMV and an unidentifiable second virus[99] have been considered. More probably, these are only secondary causes, provoking the primary one of an imbalance between the immune system and endothelial cells, which seem interdependent in angiogenesis. Oncogenes have also been implicated. It seems therefore likely that Kaposi's sarcoma is an end-result of a variety of unequally-important initiating processes.[17]

CHAPTER 4
COMPARISON WITH OTHER PUBLISHED SERIES

The distribution of sarcomas with respect to morphological type has been examined in three series published after the beginning of the work described in this Dissertation. Fisher[11] examined 200 sarcomas to show the value of EM and IHC in their diagnosis. A Scandinavian group[20] reviewed 240 sarcomas selected as `high grade', and listed original and revised diagnoses, using IHC in an unspecified number. In neither case was the interpretation of `soft tissue' defined. Patients under the age of 15 were specifically excluded from the Scandinavian study. The Eastern Cooperative Oncology Group of America[21] reviewed sarcomas of adult bone and soft tissue totalling 358 (after exclusion of 66 mesotheliomas), using IHC and EM in unspecified numbers. In this series, `soft tissue' specifically included gastrointestinal tract, and uterus.

The form in which the data is presented reveals the details of specific alterations made on review in the Scandinavian paper. The American gives only the numerical alteration made on review to each sarcoma category. Fisher's diagnoses are all primary.

Table 4 shows final diagnoses as a rounded percentage of the total for the following series:

TABLE 4

SARCOMA TYPES AS % OF TOTAL

(in order of SNOMed listing)
(Cases as % of total in four independent series)

	Cape Town		America[21]	Scandinavia[20]	England[11]
TOTAL CASES	510[A]	67[B]	257[C]	226[D]	200
Sarcoma NOS	15	4	3	5	4 %
Epithelioid	1	1	<1	<1	4
Fibro-	5	4	5	2	2
MFH*	14	21	16	42	28
DFP*	7	12	-	-	-
Lipo-	12	4	8	9	19
Leiomyo-	5	9	38	9	4
Rhabdomyo-	8	6	<1	<1	13
MM*	<1	0	<1	2	-
SS*	7	7	5	15	10
CCS*	2	1	-	<1	1
Angio-	2	0	1	1	2
MHE*	<1	3	-	-	-
Kaposi's	10	3	<1	-	-
MHP*	1	3	4	2	<1
Osteo[E]-	<1	0	>4	1	2
Chondro[E]-	<1	0	>5	2	2
EGCT*	<1	1	-	-	-
Ewing's[E]	1	3	3	<1	3
MPNST*	7	10	5	6	6
MGranCT*	<1	0	<1	-	-
ASPS*	1	4	2	-	2

* Acronyms - see p v

A - early (reinterpreted) plus middle plus late series combined, as discussed in Chapter 2 and shown in Fig. 1

B - early (reinterpreted) cases only, as shown in Table 2

C - Adult cases only, not restricted to soft tissue. Includes gastrointestinal tract, uterus and bone.

D - Adult cases only.

E - Extraskeletal (except in American series).

Figures are rounded to the nearest integer.

our series of 67 reinterpreted cases 1960-4 as listed in Table 1.

our grand combined series (also shown in Fig. 1) of 510 cases (of which the 67 cases just referred to form a part. The other 443 cases have not been reinterpreted; 289 are from 1971-82 [1979 omitted] and 154 from 1986-90, as listed in Table 1).

the American series of 257 final reinterpreted diagnoses.

the Scandinavian series of 226 final reinterpreted diagnoses.

Fisher's series of 200 diagnoses.

Inter-series comparison must take into account that the selection criteria are not the same in each, and the fact that our own review is the only one to feature historical material for which some current diagnostic categories were originally nonexistent, so that the diagnostic turbulence it refelects will automatically be more severe.

Table 5 shows the proportion of original diagnoses in each sarcoma category which were revised on reappraisal. This is also expressed as a percentage where 5 or more cases were reviewed. The figures given for our study are those of the 78 re-examined cases of 1960-4 (see Table 7)

Table 6, using the data of Table 5, groups sarcomas into categories according to the instability of diagnosis as expressed by likelihood of revision on review. There appeared to be four natural categories as follows:

TABLE 5

SARCOMA DIAGNOSES REVISED ON REVIEW

(in order of SNOMed listing)
Proportion of cases and (percentage of cases[A])
in three independent series

	Cape Town		America[21]		Scandinavia[20]	
TOTAL NUMBER	55/78	(70)[B]	101/358[C]	(28)	68/240[D]	(28)
Sarcoma NOS	30/32	(94)	22/30	(73)	13/16	(81)
Fibro-	10/11	(91)	14/27	(52)	8/11	(73)
MFH*	-		10/51	(20)	14/89	(16)
DFP*	0/4		-		-	
Lipo-	2/5	(40)	6/26	(23)	6/25	(24)
Leiomyo-	1/4		15/112	(13)	8/24	(33)
Rhabdomyo-	2/4		10/12	(84)	5/7	(71)
MM*	1/1		F		1/5	(20)
SS*	1/2		4/16	(25)	7/34	(21)
CCS*	-		-		0/2	
Angio-	-		6/9	(67)	1/3	(33)
MHE*	-		F		-	
Kaposi's	1/3		F		-	
MHP*	0/2		2/11	(18)	0/5	(0)
Osteo[E]-	-		5/14	(36)	1/2	
Chondro[E]-	-		0/14	(0)	0/4	
EGCT*	<1		F		-	
Ewing's[E]	-		0/7	(0)	1/1	
MPNST*	5/6	(82)	3/16	(19)	3/12	(25)
MGranCT*	-		F		-	
ASPS*	0/2		0/4		-	

* Acronyms - see p v

A - shown only where five or more cases reviewed

B - 1960-4 cases only, as in Table 1

C - Adult cases only, not restricted to soft tissue. Includes gastrointestinal tract, uterus and bone.

D - Adult cases only, restricted to soft tissue.

E - Extraskeletal (except in American series).

F - Not determinable from data as published.

TABLE 6

INSTABILITY OF SARCOMA PRIMARY DIAGNOSIS TO AMENDMENT

in three independent series

	America[21]	Scandinavia[20]	Cape Town
Sarcoma NOS	VU	VU	VU
Rhabdomyo-	VU	VU	**U**
Angio-	VU	S	
Fibro-	**U**	VU	VU
MFH*	S	S	
Lipo-	S	S	**U**
Leiomyo-	S	S	s
SS*	S	S	u
MHP*	**S**	VS	vs
Osteo[E]-	S	u	-
MPNST*	S	S	**VU**
Chondro[E]-	VS	vs	-
Ewing's[E]-	VS	vu	-
ASPS*	vs	-	vs
MM*	-	S	vu
DFP*	-	-	vs
Kaposi's	-	-	s

VS (Very Stable) S (Stable)
U (Unstable) VU (Very Unstable)

(as defined on p 31)

Bold type indicates results which are discordant in one series (in which 5 or more examples were reviewed) when compared with the two others.

Lower case type indicates series which contain fewer than five examples reviewed, and for which categorisation is therefore hardly justified.

* Acronyms - see p v

E - Extraskeletal (except in American series).

Very Unstable (VU): >63% revised

Unstable (U): 38-63% revised

Stable (S): 13-37% revised

Very Stable (VS): <13% revised

The American series was used in setting the cutoff points, as it contained the largest number of cases. (Lower case type shows a tenuous conclusion based on less than 5 cases. Bold type indicates results where one series appears to differ rather strikingly from those in the other two).

Comparing the incidence of various sarcoma types in the 5 series shown in Table 4, there is substantial agreement. The excess of leiomyosarcomas and bone tumours in the American series is explained, as already noted, by topographically unrestricted selection criteria.

MFH and SS are relatively over-represented in the Scandinavian series, and MFH, liposarcoma and rhabdomyosarcoma in the English.

Our own main series shows an excess of sarcoma NOS, but only in that part of it which has not been totally rescrutinised with benefit of IHC; the subseries for which this has been done is in line with others' findings. Our main and sub-series, like the English one, contains a higher percentage of rhabdomyosarcoma because paediatric cases are included. Ours also show a striking incidence of Kaposi sarcoma, as already discussed in Chapter 3.

Although our main series has approximately the same percentages of MPNST (7%) and liposarcoma (12%) as found by

others, these percentages in the subseries are somewhat higher in the case of MPNST (10%) and significantly lower in the case of liposarcoma (4%). We argued, in Chapter 3, that the relative abundance of liposarcomas, amounting to 18% of the 1971-82 tumours (Table 2), might be the result of misdiagnosis of other myxoid sarcomas, yet this figure is even exceeded by the English one (Table 4), which at 19% is twice as large as found by the Scandinavian and American authors.

One attributes the excess of MHE and ASPS our subseries to fluctuations in small numbers which do not warrant further discussion.

In the Scandinavian series, the most common missed diagnosis was MFH in cases reported as: sarcoma NOS, liposarcoma, leiomyosarcoma, rhabdomyosarcoma and MPNST. In cases reported as MFH, the most common missed diagnosis was one of benign tumour. (However, the extraordinary proportion of MFH in this series - see Table 4 - suggests possible overdiagnosis).[15] In our review of 1960-4 cases, we too found MFH to feature in the revisions of sarcoma NOS (8 out of 32), leiomyosarcoma (1 out of 4), rhabdomyosarcoma (1 out of 4), and MPNST (1 out of 6), and also found it in fibrosarcoma as construed in that era (3 out of 11)(Table 7).

CHAPTER 5
A RE-EXAMINATION OF 78 SARCOMAS REPORTED IN 1960-4

It is said[22] that 4-10% of neoplasms routinely examined present diagnostic difficulties, many of which are not intrinsic, being related to poor sampling, preservation, or lack of clinical data. Of the intrinsic difficulties, there are morphology and pattern-type problems, and discordant IHC.

Immunohistochemistry is only secondarily a matter of interest in this dissertation, although the immunohistochemistry of intermediate filaments[22] has made great strides possible in the diagnosis of sarcomas,[23] to the point where choice of antibodies requires careful reflection.[24] The use of CD (cluster of differentiation) Antigens rather than intermediate filaments as tissue markers in the field of sarcomas is still in its infancy, but a start is being made here too.[25]

The diagnostic problems resulting from IHC conflicts are currently in great vogue, as the method enters its mature phase. Numerous publications have been spawned, and retrospective analyses been conducted. For example, the many reports of cytokeratin-positivity in sarcomas drew the comment that "those...who have not encountered widespread cytokeratin reactivity in mesenchymal neoplasms, and those...who are struggling to interpret the significance of others' experiences, are left to view this debate much as Alice

pondered the Cheshire cat: a smile with seemingly little substance. But let us be wary that the cat is not laughing at us". The comment achieves the distinction of being as enigmatic as its metaphor.[26]

Of greater interest is the morphological aspect of diagnostic disagreement. Comparisons between current (reassessed) diagnosis and original diagnosis for the 78 1960-4 sarcomas in the study are presented in Tables 7 and 8.

Table 7 shows the sources of the current diagnoses, and Table 8 the changes made to the original diagnoses, which are also shown diagramatically for the relatively large subgroups of original diagnoses of Sarcoma NOS in Fig. 3 and of Fibrosarcoma in Fig. 4. It must be remembered that none of the qualifications have been entered in these Tables that would have accompanied the report of each case, and not all diagnoses have equal weight: diagnoses for which there exist(ed) serious reservations were entered as `sarcoma NOS', but even within specific categories, some cases were diagnosed as certain, others as probable examples.

The features used in an attempt to characterise each diagnostic category of sarcoma are summarised below, at the beginning of the relevant subsections. The criteria are presented collectively in Chapter 6 and Figs 5. Where illustrative, reference is made to what are considered to be previously miscategorised lesions.

TABLE 7

PREVIOUS vs CURRENT DIAGNOSES
COMPARED FOR 78 1960-4 SARCOMAS

Previous Diagnosis	No	Currently Diagnosed As
Sarcoma NOS	32	Sarcoma NOS (2), MFH* (8), MPNST (4), Leiomyo-(3), Rhabdomyo- (2), Ewing's^{E} (1), EGCT* (1), Epithelioid sarcoma (1), CCS* (1), Fibro-(1), SS (1), ASPS (1), Spindle carcinoma (3), Neurilemmoma (1), Proliferative myositis (1) Nodular fasciitis (1) See Fig. 3
Fibro-	11	Fibro-(1), MFH (3), DFP (3), Sarcoma NOS (1), SS (1), MPNST (2) See Fig. 4
DFP*	4	DFP (4)
Myxo-	2	Myxoma (1), Nodular fasciitis (1)
Lipo-	5	Lipo-(3), Myxoma (1), SS (1)
Leiomyo-	4	Leiomyo-(3), MFH (1)
Rhabdomyo-	4	Rhabdomyo-(2), MFH (1) Epithelioid haemangioendothelioma (1)
MM*	1	Myositis ossificans (1)
SS*	2	SS (1), Ewing's^{E} (1)
Kaposi's	3	Kaposi's (2), MHE* (1)
MHP*	2	MHP (2)
MPNST*	6	MPNST (1), Fibro- (1), MFH (1), DFP (1), SS (1), Clear cell sarcoma of kidney (1)
ASPS*	2	ASPS (2)
TOTAL	78	

* Acronyms - see p v

E - Extraskeletal

TABLE 8

CURRENT vs PREVIOUS DIAGNOSES
COMPARED FOR 78 1960-4 SARCOMAS

Current Diagnosis	No	Previously Diagnosed As
1. SOFT TISSUE SARCOMAS		
Sarcoma NOS	3	Sarcoma NOS (2), Fibro- (1).
Epithelioid	1	Sarcoma NOS (1).
Fibro-	3	Fibro- (1), MPNST (1), Spindle (1)
MFH*	14	Sarcoma NOS (8), Fibro- (3) Leiomyo- (1), MPNST (1), Rhabdomyo- (1).
DFP*	8	DFP (4), Fibro- (3), MPNST (1).
Lipo-	3	Lipo- (3).
Leiomyo-	6	Leiomyo- (3), Sarcoma NOS (3).
Rhabdomyo-	4	Rhabdomyo- (2), Sarcoma NOS (2).
SS*	5	SS (1), Sarcoma NOS (1) MPNST (1), Fibro- (1), Lipo- (1).
CCS*	1	Sarcoma NOS (1).
MHE*	2	Rhabdomyo- (1), Kaposi's (1).
Kaposi's	2	Kaposi's (2).
MHP*	2	MHP (2).
EGCT*	1	Sarcoma NOS (1).
Ewing's^{E}	2	Sarcoma NOS (1), SS (1).
MPNST*	7	MPNST (1), Sarcoma NOS (4), Fibro-(2)
ASPS*	3	ASPS (2), Sarcoma NOS (1).
TOTAL	67	
2. RENAL SARCOMA		
Clear cell renal sarcoma	1	MPNST (1).
3. NONSARCOMAS		
Spindle carcinoma	3	Sarcoma NOS (2), Spindle Sarcoma (1).
Nodular fasciitis	2	Sarcoma NOS (1), Myxosarcoma (1).
Myositis ossificans	1	MM*.
Proliferative myositis	1	Sarcoma NOS.
Neurilemmoma	1	Sarcoma NOS.
Myxoma	2	Lipo- (1), Myxosarcoma (1).
TOTAL	11	

* Acronyms - see p v

E - Extraskeletal

Fig 3 **Sarcomas (NOS)**

32 cases from 1960-4 reinterpreted

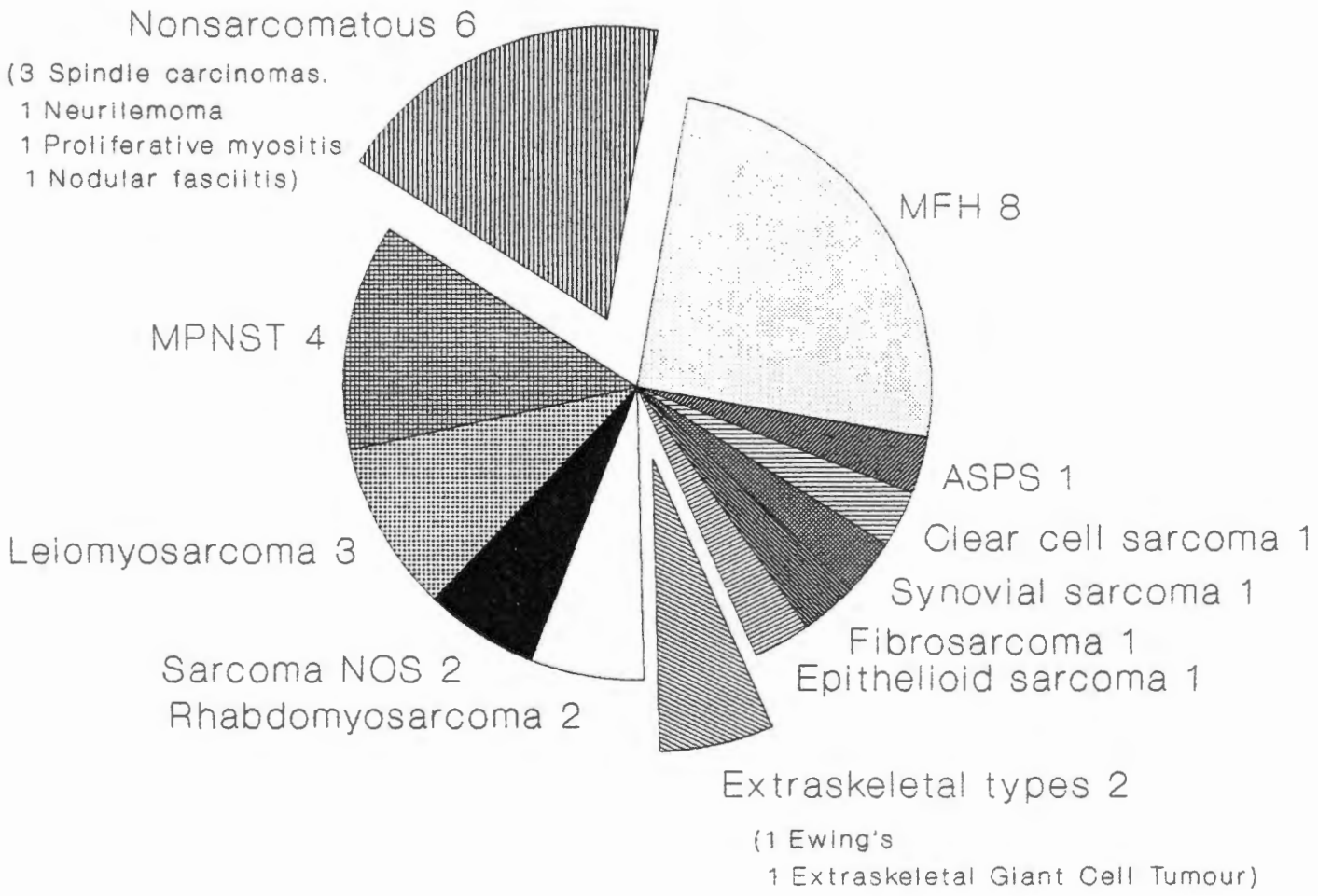
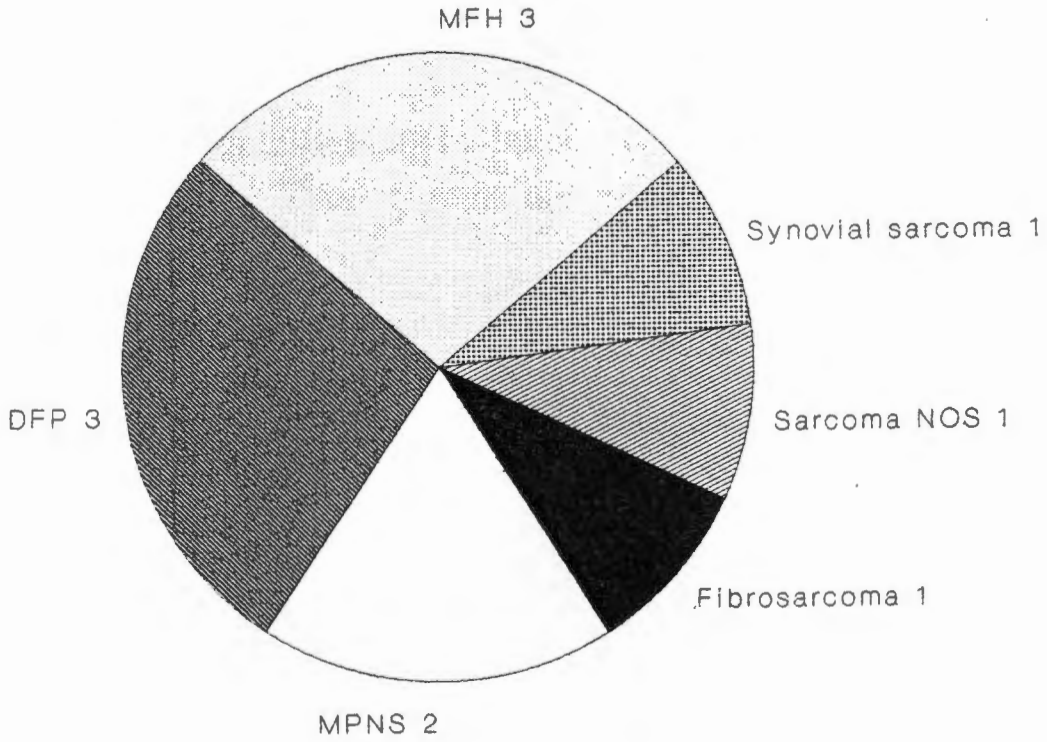


Fig 4 **Fibrosarcomas**

11 cases from 1960-4 reinterpreted



I SOFT TISSUE SARCOMAS

1. Sarcoma NOS (3 cases)

This is a default diagnosis, and the fact that only 3 were made in the period supports Fisher's figure[11] of only 3.5% of sarcomas remaining unclassifiable after recourse to IHC and EM where necessary. It possibly also reflects a greater readiness to make a committed diagnosis when clinical action is not to be undertaken; the extent of this is difficult to assess, but it undoubtedly induces a subconscious freedom.

All three cases show the problem of diagnosis of a spindle-cell lesion without qualifying features. All showed a sweeping pattern for which the differential is wide. Two cases had been diagnosed as sarcoma NOS originally. In both, the cells were spindled, some being rather epithelioid, without giant cells. One [7025/63] was in addition nucleolated, and vascular, with an impression of `staghorn' vessles. The diagnoses considered for this were carcinoma, melanoma and, giving weight to the vessels, malignant haemangiopericytoma, but only enough tissue remained in the block to show vimentin positivity and cytokeratin negativity. The other case [6293/62] was rather myxoid and had a suggestion of whorling, so that a diagnosis of MPNST was favoured, but no block was available.

The third case [7749/61], related to the mandible, originally diagnosed as a low-grade fibrosarcoma, was likewise

vascular, but with fibrillar stroma, plump spindle cells and slightly myxoid areas. A monophasic fibrous synovial sarcoma was favoured on reassessment, but the specimen was poorly preserved (possibly because of decalcification procedures) and IHC uniformly negative.

The conclusion is that in poorly differentiated tumours, an analysis of patterns and stroma can be insufficient in the absence of the subtle features which confirm a diagnostic suspicion. It can also sometimes be questionable whether a low-grade tumour is malignant at all; epithelioid and nucleolated tumours, especially, raise doubts about mesenchymal origin which are best put to the test with vimentin.[27] The converse is not true: epithelial markers are positive in carcinosarcoma (sarcomatoid carcinoma).

2. Epithelioid sarcoma (Figs 5, 5.4) (1 case)

Pattern: epithelioid

Stroma: fibrillar

Cells: granular epithelioid

Additional features: +/- necrosis, inflammatory cells, calcification, papillary areas, spindled areas, sclerosis, nodularity.

The criteria, including necrosis, inflammatory cells, spindling and nodularity are met by the single example [6151/61], originally thought to be vascular. The stroma was felt to be more fibrillar than vascular on reassessment, and a stain for Factor 8 marked entrapped capillaries rather than

tumour. (Cytokeratins and neurofilaments have been reported in epithelioid sarcoma).[28] A more recent differential diagnosis to be considered for any epithelioid sarcoma would be malignant rhabdoid tumour of soft tissue.[29]

Epithelioid sarcoma has been reported to develop diffuse bone marrow metastases and an associated leukemoid reaction.[30]

3. Fibrosarcoma (Figs 5, 5.2, 5.3, 6) (3 cases)

Pattern: arranged (herringbone)/sweeping

Stroma: hyaline

Cells: plump spindle

Additional features: inflammatory cells (infantile form), +/-necrosis, sclerosis

The criteria were well met by one of the three cases, originally diagnosed as a spindle cell sarcoma [1656/64]. Another [3022/61] had been diagnosed as malignant and probably of neurogenic origin. It was true that the pattern was arranged, being slightly whorled, but it was more strikingly fascicular, with definite `herringbone' areas. The cells were plump spindle, and the stroma hyaline without showing myxoid or vascular properties. IHC for S100 was, as expected, negative, and the lesion classified as a probable fibrosarcoma.

The third case [7560/63], occurring in relation to the mandible of a child, illustrated the sometimes decisive value of a clinical history. The pattern was sweeping, with a loose, though not myxoid, fibrillar appearance and hyaline fascicles

coursing through it. It also contained numerous inflammatory cells, compatible with possible infantile fibrosarcoma. This diagnosis was preferred to an odontogenic neoplasm because of the age of the patient.

The reluctance to diagnose fibrosarcoma perhaps represents too far a swing of the pendulum away from this once common entity (see Fig. 4) as a result of a discouraging awareness of MFH and monophasic synovial sarcoma.[31]

4. Malignant fibrous histiocytoma (Figs 5, 5.1-3, 6)

(14 cases)

Pattern: arranged (storiform)[32]/disarranged/sweeping

Stroma: myxoid/hyaline/fibrillar/vascular

Cells: plump/slender spindle. Epithelioid in pleomorphic MFH

Additional features: multinucleate giant cells, inflammatory cells, +/- necrosis

Seven of the 14 cases were typical, and met the major criteria of storiform pattern with giant cells. Three had previously been called fibrosarcomas, [8576/60, 9054/61,1722/63] and 4 sarcomas NOS [4724/60, 5490/61,5679/62,7654/64]. Difficulties with the diagnosis arise in the absence of areas with an arranged pattern.

Cases with disarranged pattern (i.e. not conclusively storiform):

Three of the sarcomas NOS [3589/61,3784/61,6043/62] showed a predominantly disarranged pattern (though with giant and inflammatory cells present in accord with MFH). The possibility of spindle-cell carcinoma and melanoma was raised because of their epithelioid cells and nucleolation. It was excluded by IHC (vimentin positivity, S100 and cytokeratin negativity).

Another sarcoma NOS [3750/64], and a tumour tentatively diagnosed previously as a rhabdomyosarcoma [6213/61], showed disarranged patterns, and giant cells, but no inflammatory cells. They had fibrillary stroma and very plump and rather epithelioid cells, highly suggestive of pleomorphic rhabdomyosarcoma. However, PTAH staining revealed no cross-striations, desmin IHC was negative (except in the second case where the cells marking were entrapped muscle), and IHC with a histiocytic marker (Mac387) focally positive.

A case previously called leiomyosarcoma [5581/64], with a disarranged pattern and giant cells, showed hyaline stroma supporting the diagnosis. Inflammatory cells were sparsely present, however, and the cells rather epithelioid for the diagnosis. Some of the spindle cells were also rather slender. The preferred diagnosis of MFH was supported by negative desmin IHC and positivity with Mac387.

Case with sweeping/?arranged (whorled) pattern, doubtfully storiform:

Another case [1878/63], previously called neurogenic sarcoma, had, in agreement with this diagnosis, a suggestion of whorling, and densely-packed epithelioid and plump spindle cells, myxoid and hyaline areas alternating. Inflammatory and giant cells were not present. However, S100 was negative and a histiocytic marker (Mac387) positive.

The cell of origin of the MFH continues to provoke controversy, and that it is histiocytic is strongly disputed.[33] It is usually vimentin-positive, but has been reported in some instances to express cytokeratin,[34,35,36,37] neurofilament[35,35,37] and even desmin.[35,36] The angiomatoid variant has recently been reviewed,[38] and evidence from IHC led to support myoid differentiation for it on one hand[39] and histiocytic origin on the other.[40] A warning has been made concerning the differentiation from an atypical pseudosarcomatous variant of cutaneous benign fibrous histiocytoma,[41] and a case reported of multicentric MFH.[42] There appears to be a correlation between the histologic grading of MFH and the extent of its Ki-67 staining.[43] The relationship of subtype of MFH to prognosis has been investigated in a large recent series.[44]

5. Dermatofibrosarcoma protuberans (Fig. 5, 5.2, 6) (8 cases)

Pattern: arranged (storiform)

Stroma: hyaline/vascular/myxoid/fibrillar

Cells: slender spindle

Additional features: nodular. Giant/inflammatory cells sparse.

Of the 8 cases, 6 were typical and met the criteria of a storiform pattern with low-grade features. Of these, 2 had originally been diagnosed as DFP [2193/61,10007/62], 3 as fibrosarcomas [7734/60,2775/61,2343/63], and 1 as a low grade sarcoma of possible neurogenic origin [89/61].

The other 2 cases, because of pattern, were not quite as straightforward, although diagnosed originally as DFP. One [2473/61], having an arguably storiform pattern with hyaline stroma and without giant or inflammatory cells, was quite cellular and areas of it sweeping rather than arranged. This raised the possibility of a fibrosarcoma or leiomyosarcoma. (DFP with fibrosarcomatous areas is a recently-described entity,[45] but in favour of the diagnosis of DFP, the spindled cells were slender rather than plump, and desmin was negative. The other case [712/61] had a whorled rather than storiform pattern that suggested neural origin, but S100 was negative.

The histogenesis of DFP has recently been investigated.[46] A granular cell variant has been described.[47] The relationship to the uncommon low-grade childhood lesion of Giant Cell Fibroblastoma (GCF) has been the subject of considerable discussion,[48] and GCF has been shown to recur as DFP[49] and to

co-occur with DFP.[50] The patterns of extension into tissue of deep dermatofibromas have been compared with those of DFP to distinguish the two in the occasional cases encountered of deep dermatofibroma.[51]

6. Liposarcoma (Figs 5, 5.1, 5.2, 5.4, 5.5, 6) (3 cases).

Pattern: lacy (well-differentiated, myxoid, round cell, sclerosing)
disarranged (pleomorphic)
epithelioid (round cell,)
arranged (sclerosing)

Stroma: myxoid/vascular (well-differentiated, myxoid, round cell, sclerosing, pleomorphic)
hyaline (sclerosing)
fibrillar (pleomorphic)

Cells: spindled (well-differentiated, myxoid, sclerosing, pleomorphic)
granular epithelioid (round cell, pleomorphic)
clear epithelioid (pleomorphic, epithelioid)
lipoblasts must be present

Additional features: giant cells in pleomorphic liposarcoma
prominent vascularity in all forms.

All 3 cases were typical and met the criteria, 2 being myxoid [3470/62,5997/62] and one well differentiated [5694/61]. Previous diagnoses of all were in agreement.

Liposarcomas have not been the subject of as intensive publication recently as have some other sarcomas, but one study of 111 cases of various types showed that myxoid liposarcoma has the best prognosis and pleomorphic the worst, with well-differentiated being intermediate. The need was expressed for a category of `atypical lipoma' for diverse non-retroperitoneal lesions of adipose tissue with good prognoses.[52] In another study of 127 cases, however, well-differentiated liposarcoma had best prognosis, followed by myxoid, and pleomorphic. Fibroblastic and lipoblastic variants were recognised in this study, fibroblastic carrying a prognosis akin to that of pleomorphic, and lipoblastic having the worst prognosis of all.[53] (Round cell liposarcomas were not included as such in either study).

7. Leiomyosarcoma (Figs 5, 5.1-5, 6) (6 cases)

Pattern: sweeping/disarranged/rarely arranged (palisaded)
epithelioid/lacy (epithelioid variant)

Stroma: hyaline/fibrillar/vascular/myxoid

Cells: plump spindle
epithelioid (epithelioid variant)

Additional features: +/- giant cells, necrosis

Of the 6 cases, 3 [993/62,5468/63,8906/64] which had previously been called leiomyosarcomas met the criteria without difficulty. Another case [1001/62], previously called sarcoma NOS, whilst meeting the criteria for leiomyosarcoma,

was situated in superficial dermis and contained both inflammatory and nucleolated cells, and it was necessary to exclude melanoma by demonstration of negative S100. Another case previously called sarcoma NOS [2538/61], likewise meeting leiomyosarcoma criteria to the extent that the diagnosis was thought highly probable, had, in addition, vascular stroma and a slightly haemangiopericytic appearance. Though it lacked epithelioid cells, clinical data supplied included reference to vascularity, and the differential therefore had to include malignant haemangiopericytoma. Factor 8 was negative and desmin positive, establishing the lesion as a vascular leiomyosarcoma of an extremity - a highly unusual tumour.[13c]

In one other with a sweeping pattern, fibrillar-hyaline stroma, plump spindle cells and necrosis, which had been called a spindle-cell sarcoma [6347/63], leiomyosarcoma was favoured but monophasic synovial sarcoma was felt to enter the diagnosis because of absence of giant cells, and presence of hypervascularity and inflammatory cells. Calcification, however, was not a feature. IHC in this instance was unhelpful; although vimentin could be demonstrated, desmin positivity for leiomyosarcoma and cytokeratin dot-positivity for synovial sarcoma were both lacking. (The question of negative desmin results is addressed below). A diagnosis of leiomyosarcoma was eventually allocated, partly because of the necrosis and high mitotic index, but mostly because of the classic cigar-shaped nuclei.

A study of spindle-cell sarcomas with myofibroblastic differentiation has recently been published.[54] The following have been described and discussed: leiomyosarcoma of bone,[55] the special features of smooth muscle tumours of the external genitalia,[56] leiomyosarcomas of childhood,[57] cutaneous and subcutaneous leiomyosarcomas.[58] The issue of satisfactory markers for smooth and striated muscle has been constantly debated. Desmin and MSA (muscle-specific antigen) have been compared.[59] Reported incidences of desmin staining in malignant tumours of smooth and striated muscle are highly variable.[60] Because of this, the role of desmin has been critically re-examined. It was shown that although all specimens of normal muscle and rhabdomyo[sarco]ma marked with desmin, 1 leiomyoma of 13 and 8 leiomyosarcomas of 26 did not,[60] which is of relevance to one of the cases discussed above. Of equal concern are the reports of apparent co-expression of cytokeratin by smooth muscle cells.[61] A figure of 21% leiomyosarcoma positivity for cytokeratin has been reported,[26] making this the most common sarcoma (except epithelioid and synovial sarcoma, where it is expected) to mark for cytokeratin, and thereby presenting a potential source of confusion. Miettinen quotes cytokeratin and EMA positivity in 42% and 60% of leiomyosarcomas respectively.[62]

8. Rhabdomyosarcoma (Figs 5, 5.1, 5.3-6, 6) (4 cases).

Pattern: disarranged (pleomorphic)
disarranged/sweeping (embryonal)
alveolar (alveolar).
epithelioid (embryonal, alveolar)

Stroma: vascular
fibrillar (pleomorphic, alveolar)
myxoid (embryonal, alveolar)

Cells: slender spindle/granular epithelioid (pleomorphic, embryonal)
strap-like (embryonal)
plump spindle (pleomorphic)
granular epithelioid (alveolar)

Additional features: giant cells (pleomorphic),
+/- cross-striations (embryonal)
+/- glycogen/`spiderweb' cells

Of the 4 cases, 2 [9534/62,8535/63] originally diagnosed as rhabdomyosarcomas met the criteria, being disarranged with myxoid stroma, strap-like cells and cross-striations, and were accepted as embryonal, of the botryoid subtype (subepithelial, cambium layer).

Another case [5698/63] diagnosed as sarcoma NOS in each of its four separate presentations was, in the best specimen [2268/63], an embryonal rhabdomyosarcoma. No block for this specimen is available, and the other specimens were more difficult to be sure of, with some areas being myxoid and some

fibrillary. In the differential between other pleomorphic tumours and leiomyosarcoma, only the latter could be discounted (for lack of hyaline stroma). It was necessary to show positive MSA staining to resolve the question. (Desmin was twice negative).

The fourth case [3327/61], diagnosed as sarcoma NOS, was densely cellular, vascular, with little stroma, and sweeping in pattern. Without stroma to classify as hyaline or myxoid, the differential diagnosis would have been wide (see Fig. 5.3). However, the cells were in places strap-like, and PTAH stain showed a few with debatable cross-striations. Desmin was positive, though not emphatic, MSA acceptable.

The question of poor results with desmin in some of these historic cases where muscle origin was firmly suspected has already been mentioned. Truong[60] experienced no difficulty with desmin in relation to benign and malignant lesions of striated muscle. Another series reports reliability of the marker in 59 childhood rhabdomyosarcomas.[63] However, our own problems have been experienced elsewhere[64] in relation to `very primitive rhabdomyosarcomas'. It is also probable that original fixation may hold part of the explanation in our cases, as pointed out in Chapter 2. A higher percentage (94%) of positive marking of rhabdomyosarcomas for desmin was obtained from cryostat sections than from formalin- or alcohol-fixed sections (77%) in another study, which noted better staining when the tissue was alcohol-fixed.[65] (It also reported muscle antigen positivity in a variety of other

unrelated lesions: Wilms', rhabdoid and peripheral primitive neuroectodermal tumours, MFH, fibromatosis and myositis ossificans)

Other immunohistochemical work on striated muscle that is of interest concerns the distribution of actin isoforms in sarcomas,[66] the expression of cytokeratin,[67,68] and of S100[68] by rhabdomyosarcoma. A rather neat use of an antibody from myasthenic patients which can distinguish striated from smooth muscle has been reported.[69]

Prognosis of rhabdomyosarcoma in children has been related to anaplasia.[70] Pleomorphic rhabdomyosarcoma is said to be rare in adults over 30, and the diagnosis is more likely to be MFH or leiomyosarcoma. IHC is strongly advocated in such cases.[71] Miettinen, on re-examining 25 cases of adult rhabdomyosarcoma by IHC and EM, could confirm them in only 2 (in accord with the instability noted for this diagnosis in adults as recorded in Tables 5 and 6), and he stresses the rarity of this tumour in patients over the age of 40.[72] A series of head and neck rhabdomyosarcomas in adults between the ages of 18 and 36 has been published.[73] Rhabdomyosarcoma is the fourth commonest sarcoma of the oral/paraoral region (after osteo-, fibro- and chondrosarcoma) and the second commonest (after osteosarcoma) in patients under 20.[74]

In experimentally-induced rhabdomyosarcoma, MFH-like areas have been seen, and the presence of MFH-like foci in well-defined non-fibrohistiocytic sarcomas as evidence of de-differentiation is being increasingly reported.[75]

[9.Malignant mesenchymoma (0 cases).

This is a diverse and uncommon category, a minor part of which is two sarcomas (one generally being liposarcoma) comprising one lesion. More usually the term refers to a sarcoma (generally liposarcoma, MFH, MPNST or rhabdomyosarcoma) associated with malignant cartilage or osseous tissue.[13d] No examples were seen in the re-examined historical material (the one being so called originally was, on reassessment, thought to be more in keeping with myositis ossificans).

Malignant mesenchymoma has recently been shown, rather surprisingly, to exhibit only low-grade behaviour.[76]]

10. Synovial sarcoma (Figs 5, 5.3, 5.4, 5.6, 6) (5 cases)

Pattern: alveolar-glandular/epithelioid (glandular component)
sweeping (fibrous component)

Stroma: fibrillar/vascular (glandular component)
fibrillar/vascular/myxoid/hyaline (fibrous component)

Cells: epithelioid (glandular component)
plump/slender spindle (fibrous component)

Additional features: +/- calcification
+/- inflammatory cells (fibrous component)
+/- haemangiopericytic (`staghorn') vessels
combined glandular/fibrous features diagnostic of biphasic synovial sarcoma

Of the 5 cases, one was previously so called. This [5773/63] was an extremely interesting case occurring in the neck of a 30 year old woman. It certainly had the appropriate biphasic (but mainly glandular) appearance, with calcification moreover. However, the extremely papillary appearance of the markedly mucinous glandular component on re-assessment raised the question of metastatic adenocarcinoma and papillary thyroid carcinoma. But thyroglobulin IHC was negative (the strong positivity of CAM5.2 and CEA were equally in accord with carcinoma and synovial sarcoma). An impressive workup had originally been carried out, in which it was shown that alcian blue-positive, hyaluronidase-sensitive material was mainly in the lumena rather than intracellular, which is a diagnostic feature of SS.[13e]

Another case [4840/61], though predominantly spindled, and originally diagnosed as sarcoma NOS, had sparse glandular areas, making the diagnosis. Vimentin was positive, and cytokeratin weakly so. The EMA was not convincing because the glandular areas had been cut through on resectioning the block, leaving virtually only the spindled element. This, in contrast to the glandular component, is known to stain poorly with both epithelial markers. However, the diagnosis was felt secure on purely morphological grounds. Another [6869/64] was called a probable liposarcoma on postirradiation necrotic tissue, but an earlier specimen, diagnosed as sarcoma NOS, was confidently reassessed as a synovial sarcoma on the basis of

biphasic areas, in spite of secondary infection slightly masking this appearance.

A third case [8084/62] had understandably been called a fibrosarcoma because of a sweeping pattern, hyaline stroma, plump spindle cells and necrosis, all features shared with monophasic fibrous synovial sarcoma. However, in review, the section was noted to be vascular (indeed, mimicking a vascular sarcoma in areas) and to contain inflammatory cells, raising the question of leiomyosarcoma, MPNST, monophasic fibrous synovial sarcoma and (more remotely, since there was no storiform pattern), MFH. Accordingly, an appeal was made to IHC. The vimentin and EMA were positive, desmin, AAT and S100 negative, in agreement with a monophasic synovial sarcoma.

A fourth case [6869/64] was extremely myxoid and had been irradiated. It was diagnosed as a probable liposarcoma, but an earlier biopsy showed a glandular focus with epithelioid cells set in an otherwise spindled, vascular, somewhat fibrillar tumour containing numerous inflammatory cells. The areas with lacy pattern were attributed to fat entrapment.

The last case [292/62], occurring in the spinal cord of a woman from whom a lesion said to be a melanoma had been removed from the shoulder some years before, had been previously diagnosed as MPNST, reasonably in view of the site and since it had the features of an epithelioid MPNST (fibrillar-vascular stroma) with plump and slender spindle cells, and epithelioid cells with a suggestion of rosette formation. Necrosis was present. However, bearing in mind the

clinical history, a tentative reinterpretation was made of biphasic synovial sarcoma, the `rosettes' representing glandular differentiation. The IHC was interesting, because both S100 and EMA were positive (though neither was strikingly so). S100 positivity in both biphasic and monophasic tumours is documented[77] and accordingly it was felt that this tumour was probably a biphasic synovial sarcoma, especially in view of the weak marking by S100.

Synovial sarcoma has been reviewed,[78] and the diagnostic problems posed by the fibrous[79] and epithelial[80] types when monophasic addressed. An intravascular form has been identified.[81] Prognostic factors have been reviewed,[82] and synovial sarcoma in children and adolescents considered.[83] The interrelationship between the biphasic and monophasic subtypes has been discussed.[84]

[11. Malignant mesothelioma (Figs 5, 5.3, 5.4, 5.6, 6)

(0 cases*)

Pattern: alveolar-glandular/epithelioid (glandular component)
sweeping (fibrous component)

Stroma: fibrillar/vascular (glandular component)
fibrillar/hyaline (fibrous component)

Cells: granular epithelioid (glandular component)
plump spindle (fibrous component)

Additional features: +/- calcification
+/- inflammation
+/- necrosis
+/- papillary formation, vacuolation,
mucin lakes (glandular component)

(* This entity was specifically excluded from the study)]

12. Clear cell sarcoma (Figs 5, 5.4, 5.5) (1 case)

Pattern: epithelioid/lacy with nesting

Stroma: myxoid/fibrillar/vascular

Cells: clear epithelioid

Additional features: glycogen
+/- intracellular melanin
+/- giant cells
+/- necrosis

Only 1 case [2482/63] was found, dating from a period five years before the first description of this class of sarcoma in 1968. It had therefore correctly been called a Sarcoma NOS. It showed the classic features of clear cell sarcoma. Giant cells and necrosis were present, without intracellular melanin. S100 was positive.

Chromosomal abnormalities have been detected in 3 out of 3 cases of clear cell sarcoma examined for them, but it is too early to say whether these are characteristic.[85] The immunohistochemistry[86,87,88] and flow cytometry[88] of CCS have

been reviewed, and a study of its prognostic factors published[89].

[13. Angiosarcoma (Figs 5, 5.4, 5.6) (0 cases)

Pattern: epithelioid/alveolar

Stroma: vascular

Cells: epithelioid

Additional features: papillary `tufting' into vascular spaces
+/- necrosis

The IHC and US of angiosarcoma of the face and scalp has been reviewed.[90] An entity claimed to be distinctive, epithelioid angiosarcoma, which is allegedly often mistaken for an epithelial neoplasm, has been described,[91] and angiosarcoma may arise in Kaposi's sarcoma.[92] The IHC of angiosarcomas has been reviewed.[93]]

14. Malignant haemangioendothelioma (Figs 5, 5.3, 5.4)
(2 cases)

Pattern: epithelioid (epithelioid form)
sweeping>epithelioid (spindled form)

Stroma: vascular/hyaline(sclerosed)/fibrillar (both forms)
myxoid/(epithelioid form)

Cells: epithelioid (epithelioid form)
plump/slender spindled>epithelioid (spindled form)

Additional features: +/- intracellular vacuoles (both forms)
cavernous spaces, vascular slits,
inflammatory cells (spindled form)
+/- phleboliths (spindled form)

An example of each type was diagnosed. One [1887/63] had originally been called a Kaposi's sarcoma, which it resembled, with a sweeping pattern, predominantly spindled cells and vascular stroma, and scattered plasma cells. However, a slightly epithelioid appearance raised the possibility of angiosarcoma and haemangioendothelioma. The stroma was rather more hyaline than appropriate for angiosarcoma, and there was no tufting. The possibility of angioma had been entertained originally, because the slits were superficially rather cavernous, and in 1991, this was the feature which, even in the absence of phelobliths, favoured spindled haemangioendothelioma (in which the epithelioid cells noted are to be expected). This entity was only described in 1986.[13f] It has recently been claimed that it is not neoplastic.[94] Its co-occurrence with epithelioid haemangioendothelioma has been described.[95] Osteoclastic giant cells have been described associated with one lesion.[96]

The other [4132/60] was thought to be a possible rhabdomyosarcoma at the time the leg in which it occurred was amputated. The only material now available was not diagnostic.

However, two preliminary biopsies (the block of one now unavailable) showed a vascular tumour with all the features of an epithelioid haemangioendothelioma, being of epithelioid pattern, with vascular/hyaline stroma, epithelioid (somtimes vacuolated) cells. The appearance was classic, but confirmatory IHC was obtained from Factor 8 (desmin and cytokeratin were negative). This entity was only defined in 1982.[13g]

A Kaposi-like infantile haemangioendothelioma of the retroperitoneum has very recently been described for the first time.[97]

15. Kaposi's Sarcoma (Figs 5, 5.3, 6) (2 cases)

Pattern: sweeping

Stroma: vascular/myxoid/fibrillar

Cells: plump/slender spindle

Additional features: vascular slits
inflammatory cells (lympho-/plasma-cytes)
+/- necrosis
+/- inclusions

In both cases the original diagnosis was accepted on review. In one [8172/64], the vascular slits and mixture of spindle cells were classic, and the original diagnosis was understandably firm. In another [284/63], the spindled cells were very closely packed, and slits few, and the possibility of a spindle carcinoma was considered, though not the original

differential of fibrosarcoma (for which the stroma was insufficiently hyaline). However, IHC showed the presence of vimentin and Factor 8 and the absence of cytokeratin, confirming the original tentative diagnosis.

It has long been accepted that Kaposi's sarcoma is of endothelial origin,[98] but work continues to be published on the matter.[18]

16. Malignant haemangiopericytoma (Figs 5, 5.2-4, 6) (2 cases)

Pattern: sweeping/epithelioid/arranged (palisaded, storiform)

Stroma: vascular/fibrillar/myxoid

Cells: slender spindle/granular epithelioid

Additional features: `staghorn' vessels lined by a single layer of endothelial cells with basal lamina.

dense reticulin network

Both cases were so diagnosed originally. One [1696/62] was a classic example, of low-grade malignancy. The other [4044/61], though having a sweeping and palisaded arrangement in areas, and being prominently vascular, showed necrosis, and was particularly epithelioid, with a fibrillar appearance. Although there were myxoid areas, spindled cells were few, so that epithelioid MPNST and haemangioendothelioma entered the differential diagnosis. Against the latter, the endothelilal lining of the vascular spaces was single-layered. As with all epithelioid tumours where possible, an epithelial marker was

used to exclude carcinoma, and cytokeratin was indeed negative. So was desmin and Factor 8. Vimentin and S100 were positive. Haemangiopericytomas (soft tissue and meningeal)[100] are negative for Factor 8 (although occasional weak positivity has led to theories about intermediate forms between haemangiopericytoma and haemangioendothelioma).[101] S100 positivity is more unexpected, but has been described.[102] This case would have been the ideal subject of an ultrastructural study to differentiate haemangiopericytoma from MPNST, but on morphological grounds, the original diagnosis was regarded as probable because of the striking vascularity, ectasia, dense reticulin network and absence of a `buckled' appearance in the spindle-cell population.

The IHC of peripheral haemangiopericytoma has been compared with its meningeal counterpart, meningioma and acoustic schwannoma,[103] the distinct entity of sinonasal hemangiopericytoma reviewed[102], and hemangiopericytoma occurring in synovium described (of significance in view of the differential diagnosis of synovial sarcoma).[104]
Familial occurrence of malignant haemangiopericytoma has been described.[105]

[17. Extraskeletal osteosarcoma (Figs 5, 5.1, 5.3, 5.4, 6)

(0 cases)

Pattern: epithelioid/disarranged/sweeping

Stroma: osteoid/chondroid/hyaline

Cells: giant/plump spindle/granular epithelioid

Additional features: +/- calcification

+/- necrosis

Extraskeletal osteosarcoma has been reviewed.[106,107] The ultrastructural features of small-cell osteosarcoma have been described.[108]]

[18. Extraskeletal chondrosarcoma (Figs 5, 5.4, 5.5) (0 cases)

Pattern: epithelioid/lacy

Stroma: chondroid/myxoid

Cells: granular & clear epithelioid

Additional features: glycogen

+/- calcification

+/- multinodular pattern

An extraskeletal mesenchymal chondrosarcoma has been reported in detail.[109]]

19. Malignant extraskeletal giant cell tumour (Giant cell MFH, malignant GCT of tendon sheath) (Figs 5, 5.2-4, 6)

(1 possible case)

Pattern: epithelioid/arranged/sweeping

Stroma: fibrillar/vascular/hyaline

Cells: giant/granular epithelioid/plump & slender spindle

Additional features: storiform areas
nodularity
+/- inflammation, xanthoma cells
+/- necrosis

No cases were diagnosed originally, since this rare entity had not benn delineated at the time. One case that had been called pleomorphic sarcoma [3489/62] was felt on reassessment to be a malignant GCT, possibly extraskeletal (surviving blocks are of superficial soft tissue). Its striking vascularity was unaccompanied by any evidence of osteoid, which might have favoured a telangiectatic osteosarcoma. Bone was said to have been involved, but the location was in relation to the ankle in a 17 year old male, which would be an unusual site for a primary bone lesion.

The ultrastructure and IHC of Malignant GCT and locally destructive pigmented villonodular synovitis have been reviewed.[110]

20. Extraskeletal Ewing's sarcoma (Figs 5, 5.2, 5.4) (2 cases)

Pattern: epithelioid/arranged (rosettes)

Stroma: vascular/myxoid

Cells: granular epithelioid (`small round cell tumour'-type)

Additional features: glycogen
nested arrangement
+/- necrosis

No cases were diagnosed originally. A case called sarcoma NOS [9633/64] was thought on review to be extraosseous Ewing's because of the suggestion of rosette formation in a predominantly epithelioid, lobulated tumour. The original report had considered but excluded embryonal rhabdomyosarcoma, but this diagnosis did not enter the review differential because the cells seemed insufficiently spindled. The absence of both spindling and a sweeping pattern also spoke against other (usually more obviously) rosetted species, amongst which the chief to be considered were the neural tumours (MPNST, and primitive neuroectodermal tumours - PNETs - which, outside the central nervous system are called neuroblastoma in ganglia and peripheral neuroepithelioma or peripheral neuroectodermal sarcoma in peripheral nerve or soft tissue.[111] Ewing's sarcoma is, however, now considered to be the most primitive form of neuroectodermal tumour,[112] or at least closely related to it.[113,114] S100 is not always positive, and was negative in this case (as were EMA and desmin. Vimentin was positive). In confirmation of the diagnosis, intracellular glycogen was demonstrated.

The other current example [5892/60] had been diagnosed as a poorly differentiated synovial sarcoma. On review, it resembled the first case, except that there was no impression of rosetting, and nesting was pronounced. There were no features in the sections seen to support a synovial sarcoma, and a diagnosis of Ewing's was made with confidence.

Subsequently, glycogen was demonstrated. Vimentin was weakly positive, cytokeratin, NSE and S100 negative.

The clinicopathologic features of 42 cases of extraosseous Ewing's sarcoma have been summarised.[115] The issue of the immunohistochemistry of `small round cell tumours' is a focus of contemporary activity in research.[116,117,118] The IHC of neural adhesion molecules has been studied.[119] Childhood peripheral neuroepithelioma[120] and small round cell tumours of the chest wall[121] have been the subject of clinicopathological reviews. Cell culture of one of the latter type of tumour has demonstrated clonal cytogenetic aberrations and suggested that the tumour may be derived from primitive and pleuripotential cells which differentiate to display mesenchymal, epithelial and neural features in variable proportion.[122]

21. Malignant peripheral nerve sheath tumour

(Figs 5, 5.1-4, 6) (7 cases)

Pattern: arranged (palisaded, whorled,rosetted,plexiform)/ sweeping/epithelioid/disarranged (pleomorphic)

Stroma: myxoid/vascular/hyaline/fibrillar

Cells: `wavy' plump & slender spindled/epithelioid (greatly predominant in uncommon epithelioid MPNST)/stellate

Additional features: +/- necrosis

+/- nodular outline

+/- heterologous elements (bone/cartilage)

+/- giant cells (seldom)

+/- rhabdomyoblasts (rare `Triton' tumour)

+/- glandular differentiation

(in rare glandular MPNST)

(Neurofibrosarcoma and malignant schwannoma are considered together as MPNST; there is no sharp interface. Malignant schwannoma has less, and neurofibrosarcoma more, resemblance to a fibroblastic lesion. A neurofibrosarcomatous appearance is associated with malignancy occurring in the context of von Recklinghausen's Disease).

Of the 7 cases, only one [5412/63] was diagnosed originally. In this, the whorling was prominent, there were epithelioid and spindled cells, myxoid and hyaline areas. S100 was confirmatorily positive.

Another 4 cases had been called sarcoma NOS and one a fibrosarcoma. These on review were thought to satisfy the criteria for MPNST, especially with regard to fibrillary and myxoid stroma, and `wavy' cells (for which the usual metaphor of shoals of fish is particularly apt). Three [5468/61,4409/61,6721/62] were low-, and one [3142/64] high grade. Positive S100 IHC confirmed the diagnoses, although in one case (a myxoid lesion occurring in the jaw of a

30 year old woman), there was initially some suspicion of an ameloblastic fibroma (though the odontogenic epithelium was not well defined). The reaction with S100 was modest, attributable either to poorly-preserved material or the known variability of expression of this antigen by MPNST. The sixth case [8897/60] was of interest because it seemed possible that it might be a Triton tumour, containing suspected rhabdomyoblasts in a very anaplastic sarcoma. A speculation about muscle origin made originally had been followed up with a PTAH stain, which showed no cross-striations. The tumour was poorly-preserved, and it was not surprising to find that desmin and S100 were negative. (MSA tried throughout the period of this study was an early commercial antibody and gave generally non-contributory labelling, as in this case. It was eventually abandoned). The diagnosis of MPNST therefore rests on morphology - chiefly the myxoid and fibrillary stroma in the absence of hyaline components.

This absence of hyaline material in the seventh case seemed inconsistent with the original tentative diagnosis of fibrosarcoma [6882/60], although the pattern was sweeping and the cells spindled. But the stroma was fibrillary/myxoid, and although the material was not well preserved (the vimentin positivity was not outstanding), some of the tumour cells were S100-positive.

Some emphasis has been placed on S100 staining in this group. Yet not all MPNST are S100-positive.[13h] It has nevertheless been concluded that it is a useful marker in all

nerve sheath tumours.[123,124] The role of the perineurial cell in tumours has been receiving attention.[125] The incidental involvement of perineurial cells in some lesions leads to EMA positivity,[126] and the 50% of MPNST which are S100-negative were supposed to be derived from perineurial cells. However, spindle-cell MPNST seems to be consistently EMA-negative, thus (fortunately) separating it from monophasic fibrous synovial sarcoma.[127] GFAP and cytokeratin expression has been noted, rarely, in MPNST, which may result in diagnostic difficulties.[128,129]

A description has been given of the new entity of cellular schwannoma, which is pseudosarcomatous, and comes into the differential diagnosis of MPNST.[130] Another unusual MPNST variant has been described as a `malignant glandular triton tumour', having an adenocarcinomatous component added to rhabdomyoblastic elements in what was otherwise an MPNST.[131]

MFH is speculated to be the final common pathway of a number of `dedifferentiated tumours' such as liposarcoma and leiomyosarcoma. A newly-described variation was morphologically a typical MFH but had the annulate lamellae characteristic of Schwann cells.[132] MPNST has been shown capable of arising in ancient schwannoma,[133] schwannoma,[134] in ganglioneuroma,[135] and following radiation for unrelated tumours.[136]

The clinicopathologic features of a series of 43 cases of MPNST of the buttock and lower extremity has been published.[137]

[22. Malignant granular cell tumour (Figs 5, 5.6) (0 cases)

Pattern: alveolar (nested)

Stroma: fibrillar

Cells: granular eosinophilic epithelioid

Additional features: +/- necrosis

+/- spindled areas

Recent cases of this rare entity have been reported.[138,139]]

23. Alveolar soft part sarcoma (Figs 5, 5.6). (3 cases)

Pattern: alveolar (nested)

Stroma: fibrillar/myxoid/vascular

Cells: granular epithelioid

Additional features: glycogen

+/- prominent nucleolation

+/- intracellular crystals

+/- necrosis

This tends to be highly distinctive, and the two cases previously diagnosed were classic [953/63,8072/63].

The third case [5338/60] had been reported as a low-grade sarcoma NOS, with speculation about synovial and neural

origin. The cells were described as plump spindle. The pattern, however, was nested, initially suggesting a mitotically-active paraganglioma. This in interesting in view of the overlapping features of ASPS and paraganglioma noted in one other reported case.[140] The absence of any hyaline stroma and the fact that the cells were more epithelioid than spindled was against synovial sarcoma (and in confirmation that this was not a synovial sarcoma, IHC for EMA was negative). Paraganglioma was excluded by a negative result with Grimelius stain, and IHC which showed no marking with chromogranin. S100 was also negative, in refutation of neural origin. A positive stain for glycogen confirmed the diagnosis.

Alveolar soft part sarcoma has recently been reviewed.[141] Theories of its derivation have invoked a number of origins, including neural crest, paraganglia and skeletal muscle.[138] Most IHC studies favour rhabdomyoblastic differentiation.[142,143,144,145,146]

II RENAL SARCOMA.

Clear cell sarcoma of kidney (1 possible case)

This [3284/60] was a paravertebral tumour in an adolescent female for which the eminently reasonable suggestion of neurofibrosarcoma had been made. Some areas of the tumour were nested/alveolar, and others sweeping. The cells were spindled and stellate, and with hyalinised pseudorosettes in the nested area, in accord with the original diagnosis. However, in the nested areas, there were many strikingly clear cells with

vesicular, round nuclei and indistinct nucleoli. Stroma was fibrillar and strikingly vascular. Necrosis was present. Differential diagnoses considered were ependymal and yolk sac tumour. However, though vimentin was positive, EMA, CAM5.2, S100 and GFAP were negative, as were mucin and PAS stains. This is tentatively reclassified as a clear cell sarcoma of the kidney,[147] which would also be more in keeping with the age of the patient. Significantly in the context of the morphology, it has been hypothesised, because of the light microscopic appearances, that the Schwann cell may be the cell of origin, but this has not withstood ultrastructural investigations.

III LESIONS EXCLUDED AS NON-SARCOMATOUS

Of these cases, doubts concerning a sarcomatous nature had been expressed in 7 of them originally.

a) Carcinomas (3 cases)

Three spindle cell carcinomas were identified. Two, from the lip [2570/62], and from the tongue [9463/61] were interesting, and illustrate a difficulty which is self-evidently not altogether rare. They had been called probable sarcomas NOS, and indeed, on reassessment, leiomyosarcoma was thought to be a possibility in the first case, and pleomorphic rhabdomyosarcoma in the case of the second. However, in both, desmin was negative, although vimentin was positive. More significantly, epithelial markers (cytokeratin used in one case, CAM5.2 in the other) were strongly positive. Although

carcinosarcoma has been a term employed for such situations, it is felt better to reserve it for lesions in which there is evidence of the bimodal coexistence of carcinoma and sarcoma (in which the one cannot be seen arising from the other). However, in both, the surface epithelium was dysplastic and merged by degrees with the deeper `sarcomatous' vimentin-positive component, spindled in one case and pleomorphic in the other. Accordingly the lesions were classed as carcinoma (coexpressing vimentin - `metaplastic carcinoma' would be a suitable term), which also seemed more appropriate to the site in the case of the lip. Had the morphological progression of one element into the other not been apparent, these would have been two more apparent possible examples of cytokeratin expression by sarcomas, which is the cause of some contemporary controversy as has already been pointed out,[26] and which the semantic difficulties related to the term `carcinosarcoma' do nothing to lessen. A third case [5088/63] from the dorsum of a hand was diagnosed originally as a malignant connective tissue tumour. It apparently arose from overlying epidermis, and the cells were plump and nucleolated. Although it was thought unnecessary, positive epithelial and (in contrast to the previous cases) negative vimentin marking was exhibited.

b) Miscellaneous (7 cases)

The remainder of lesions not finally classified as sarcomas on re-assessment can be dealt with briefly.

Two myxomatous lesions originally thought to be at least `locally malignant' [5921/62,8882/62] had no lipoblastic activity, and were reassigned as myxomata, one corresponding to an intramuscular myxoma and the other to a myxoma of the jaw.[13i]

One low-grade spindle-cell lesion for which neural or smooth-muscle origin were originally proposed [3887/62] was a neurilemmoma (Schwannoma), the features causing disquiet about possible local recurrence being those due to `ancient' changes of degenerative nuclear atypia with increased vascularity, and sparse psammomatous calcification.[13j]

There were two examples of nodular fasciitis, one originally thought to be a probable sarcoma and the other a myxosarcoma. The first [8433/64] consisted of spindled, stellate and epithelioid cells in a disarranged pattern that varied from dense to loose and `feathery'. The stroma was fibrillar, vascular (some of the vessels having very thick walls) and focally very myxoid, with numerous inflammatory cells, xanthoma cells, microcysts and calcification (the diagnosis of neurofibroma or fibromatosis was made on an excision biopsy in 1965). IHC for S100, CAM5.2 and desmin was negative. The second [5786/64] was like the first except in lacking epithelioid and xanthoma cells, and calcification, but

showing keloid-like collagen which is another feature of nodular fasciitis.

A lesion [3663/61] stated to be either a pseudosarcoma or a fibrous tissue tumour not likely to behave in more malignant fashion than DFP was on reassessment called proliferative myositis with confidence. It had sweeping and disarranged patterns, with epi- and endomysial proliferation of spindled, epithelioid and giant cells. Stroma was fibrillar and hyaline, and the appearance classic.

Another lesion [2808/64] called a mixed mesodermal tumour of very low grade local malignancy, was on reassessment thought to be myositis ossificans. It had a disarranged pattern and consisted of spindled, stellate and epithelioid cells, with fibrillar, vascular and hyaline stroma showing areas of necrosis and bone formation. Low-grade background inflammation was present.

CHAPTER 6
A MORPHOLOGICAL APPROACH TO THE CATEGORISATION OF SARCOMAS

The subdivision of sarcomas into diagnostic entities is rich in scope. It provides pathologists with taxonomic fascination and debate, and is in a constant state of flux, the more so since the advent of IHC, which has raised as many questions as it has answered. Two important major contemporary texts by Enzinger & Weiss[13a] and by Hajdu[148] cover the subject of sarcoma morphology. This dissertation has been concerned with 24 diagnostic categories from SNOMed, and even so, is by no means exhaustive. Within several, such as MFH, rhabdomyosarcoma, liposarcoma, are subcategories. A major group, the mesotheliomas, and several minor ones classified as sarcomas by Enzinger & Weiss (neuroectodermal tumours, (ganglio)neuroblastoma, chordoid sarcoma [chordoma], malignant paraganglioma) and by Hajdu (ependymoma, chordoma, myeloma, granulocytic sarcoma) have been ignored. The reasons for doing so have been explained in Chapter 2.

In order to facilitate comparisons, it was felt important to reach a specific diagnosis if at all possible, even if reservations (indicated in the tabulated material by a question mark) existed. It became necessary to try and standardise diagnostic criteria, both to validate the comparisons being made, and as an exercise in itself. The art of diagnosis is one of comparing patterns. The steps suggested

to take place, not always consciously, are: aggregation of groups of findings into patterns, selection of a key finding, selection of a diagnosis and validation of the diagnosis by reference to the clinical data provided, in which site and age are of greatest importance - aetiology is practically never a factor since little is known about it. A rather similar sequence of processes has been proposed for clinical diagnosis.[149] The assessment of a histological slide presents the pathologist with myriad detail, and the first task is to reduce the size of the problem by combining sets of elementary findings into aggregate findings, taking advantage of a hierarchical approach. The next step is to generate a list of differential diagnoses, and then to prune it by comparing the known features of each with what is seen. From the final short-list, the items are compared two-at-a-time for their ability to explain the observations.

Hajdu[148] constructed tables of histological patterns, cell morphology, and stromal appearances for the sarcomas, and these were the starting-point for the Venn diagrams of this Chapter. Tables do not easily show multifactorial relationships between tumours, and each item of information can only be taken one-at-a-time, so that using data in this form to generate a list of differential diagnoses is a labyrinthine process. The power of a Venn diagram, consisting of circles each representing a particular property and containing the names of items which possess that property, is its ability to group data clearly, manageably and on multiple

levels simultaneously. Where the circles intersect, items within the overlapped areas show the properties of each of the circles making up the overlap. Thus, in the diagram of pattern combinations Fig. 5), haemangiopericytoma is easily seen to possess potentially not only the `sweeping' pattern commonly associated with it, but also to have a capacity for an `arranged' pattern and an `epithelioid' pattern, and more importantly, to resemble MPNST and GCT in this respect. In the diagram of spindle cell morphology, only a few tumours are characterised as uniquely plump-celled, and rather more as uniquely slender-celled; more complex are the major groups of sarcoma which show <u>both</u> features.

This system has been validated against the re-examined cases of this dissertation, and against other cases. It is still susceptible to modification and refinement, but has been shown to lead quickly and reasonably accurately to appropriate differential diagnoses. One must first decide whether the lesion is a neoplasm at all, and then whether benign or malignant. The ordinary classical criteria are followed: presence of atypical mitoses, high cellularity, necrosis, cellular pleomorphism and pushing or infiltrating margins all favour malignancy. Next, the sometimes difficult decision has to be made as to whether the malignant tumour is a sarcoma (i.e. truly of mesenchymal origin). With increasing frequency, this requires arbitration by IHC, and even then (with a frequency rather less increasing), ambiguity is still possible.

Having decided that a sarcoma must be retained in the list of possibilities, the first decision to be made, following Hajdu, is taken at lowest power magnification: which of six Architectural Pattern(s) does the case in hand exhibit (Fig 5)? None of them is uniquely diagnostic, even when overlapping patterns (second-order complexity) are considered. The Patterns are self-evident. The `**lacy**' consists of a web-like network, the `**alveolar/glandular**' of aggregates within septae, the `**epithelioid**' of densely-packed cells appearing to adhere to one another, the `**sweeping**' of sheets of cells which tend to align in the same direction, if only for short distances, the `**arranged**' of any kind of uniformity within which there is subordering (of which, obvious examples are the storiform nebulae seen in most MFH and the palisading in some malignant schwannomas). If no regularity at all can be perceived, the pattern is `**disarranged**'.

Having decided on the Pattern, each one generates a subsidiary Venn diagram (Figs 5.1-5.6). In these, a feature is assessed for which higher power magnification is required, namely, the stroma of the tumour. Five types: **fibrillar, hyaline**, **myxoid**, **vascular**, and **chondrified** show important discriminatory power. (Fibrillar stroma consists of the fine fibres of collagen III that would stain with reticulin. Hyaline stroma is the coarser collagen I which Masson's Trichrome can be used to emphasise).

At this point, the differential list will, under optimum conditions, have become more manageable, and further narrowing

will require ancilliary features to be sought. These include cellular morphology (spindle [Fig 6], epithelioid, giant), the presence of necrosis, calcification, inflammatory cells, staghorn vessels, cellular inclusions and so forth. Ideally, a unique diagnosis should be possible. If not, as is often the case, IHC and EM become necessary.

It cannot be too strongly emphasised that the process described is no more than useful for a provisional diagnosis. It does not at all eliminate the need for careful evaluation of the histology against the published description of the tumour being considered from an authoritative source.[13a]

Fig 5 Sarcoma Pattern Combinations

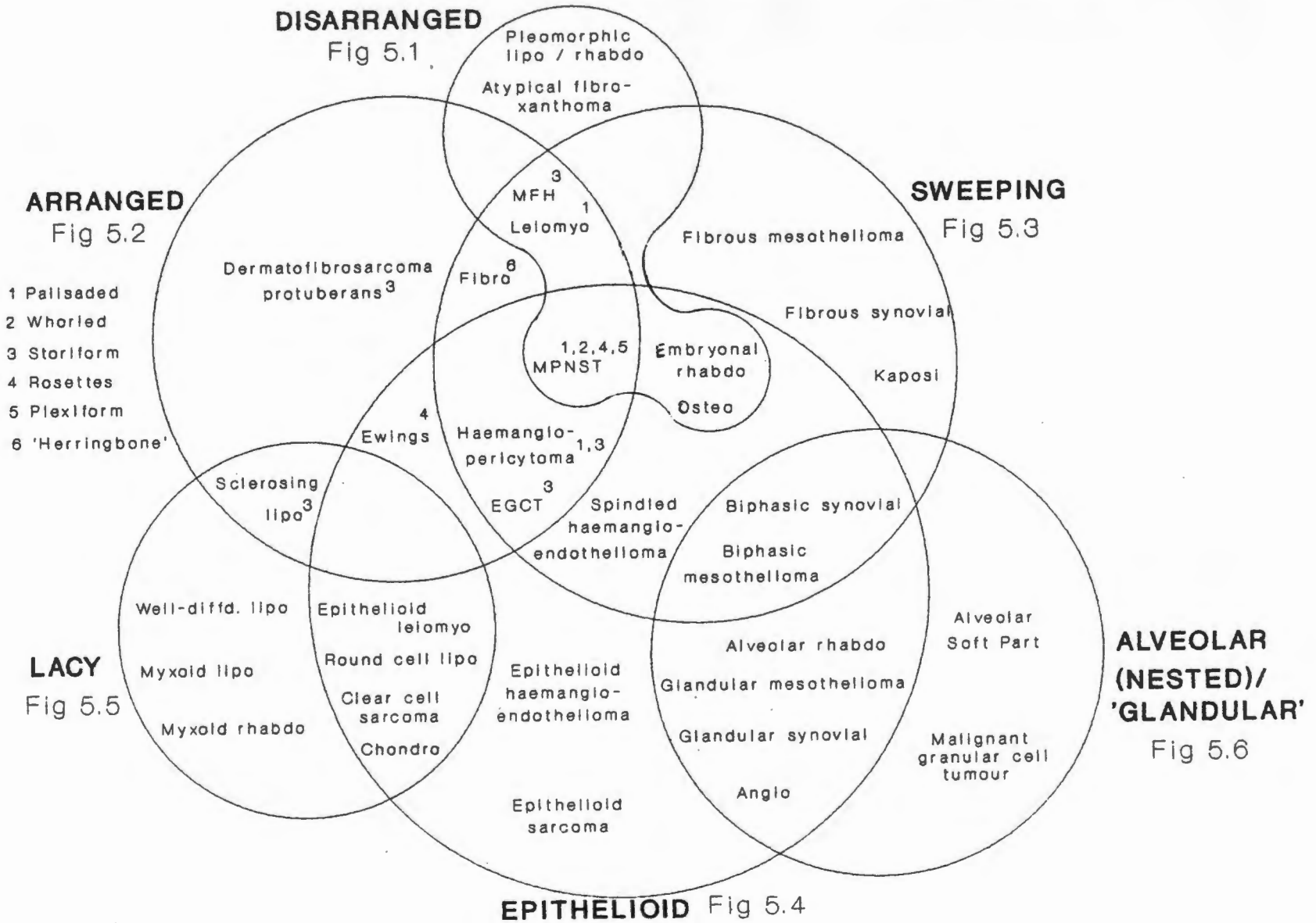


Fig 5.1 **Disarranged Pattern**

Spindled/Epithelioid Cells
Vascular. May show necrosis

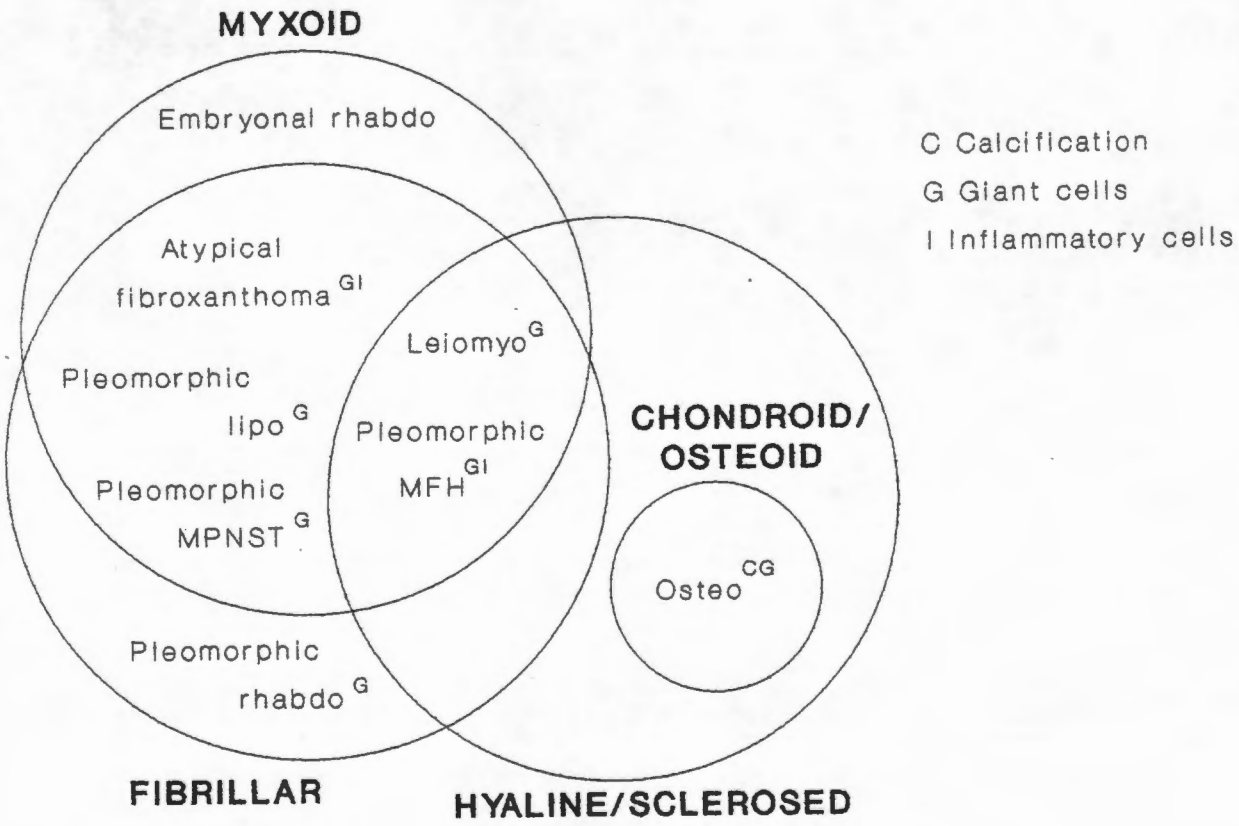
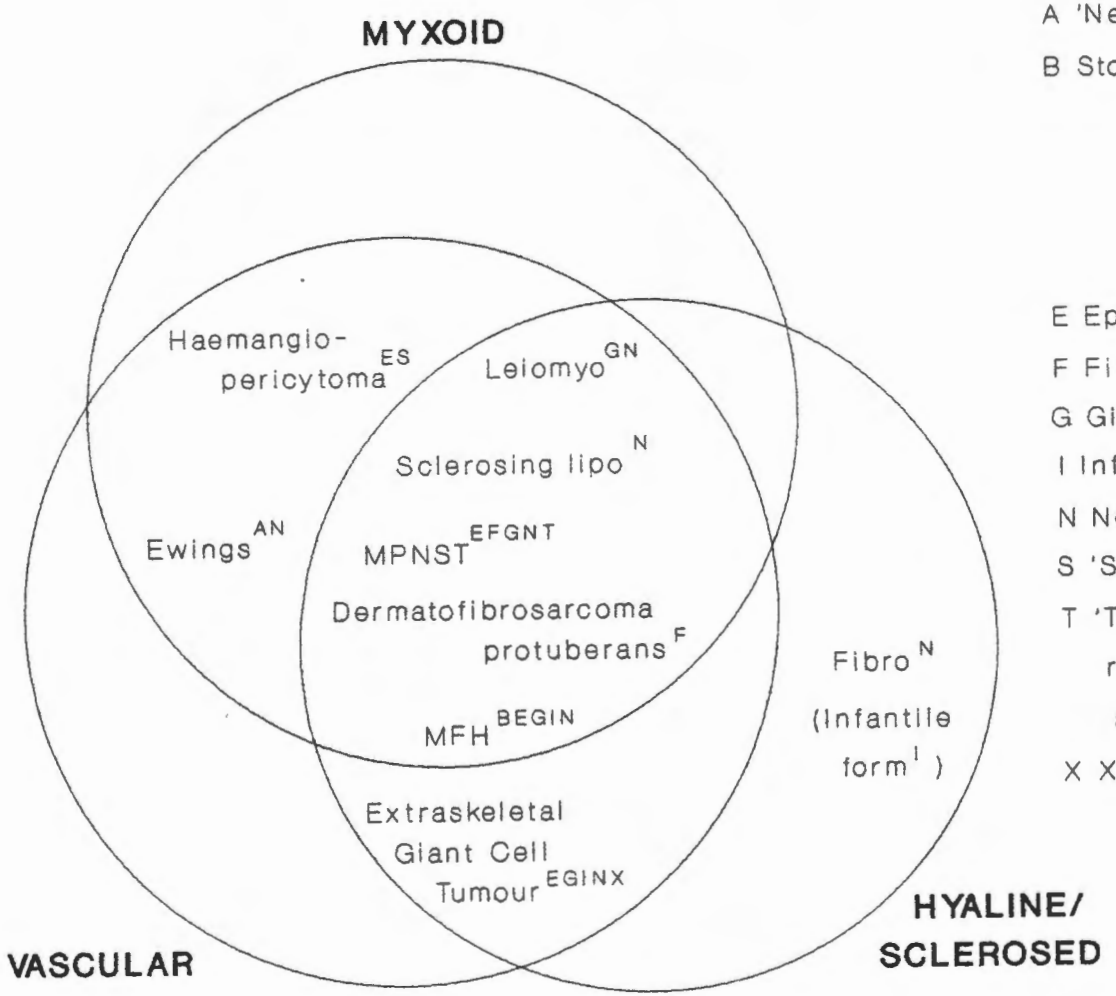


Fig 5.2 **Arranged Pattern**

(Patterns: palisaded, whorled, storiform, plexiform, rosetted, 'herringbone'. Spindled (except Ewings))



A 'Nested' arrangement

B Storiform pattern -myxoid/ inflammatory/ angiomatoid types

E Epithelioid cells

F Fibrillar stroma

G Giant cells

I Inflammatory cells

N Necrosis

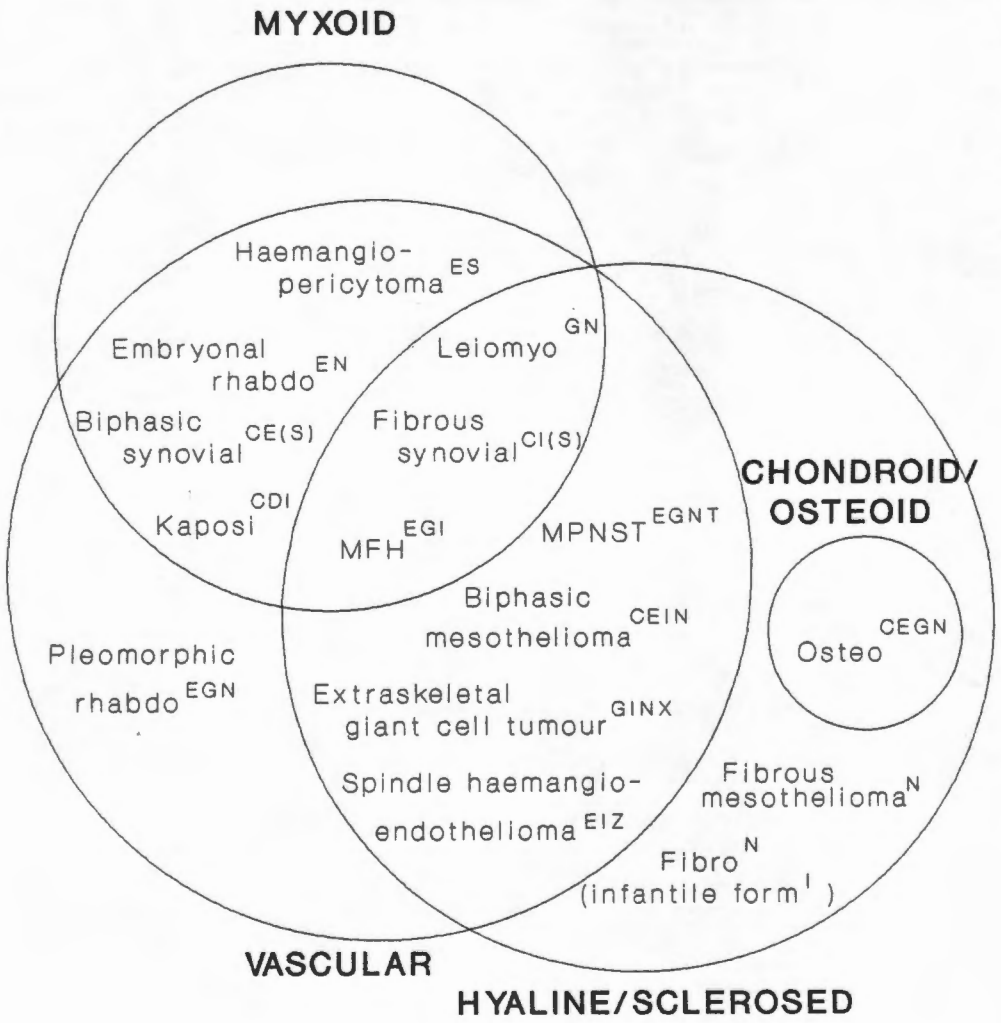
S 'Staghorn' vessels

T 'Triton' tumour if rhabdomyosarcoma admixed

X Xanthoma cells

Fig 5.3 **Sweeping Pattern**

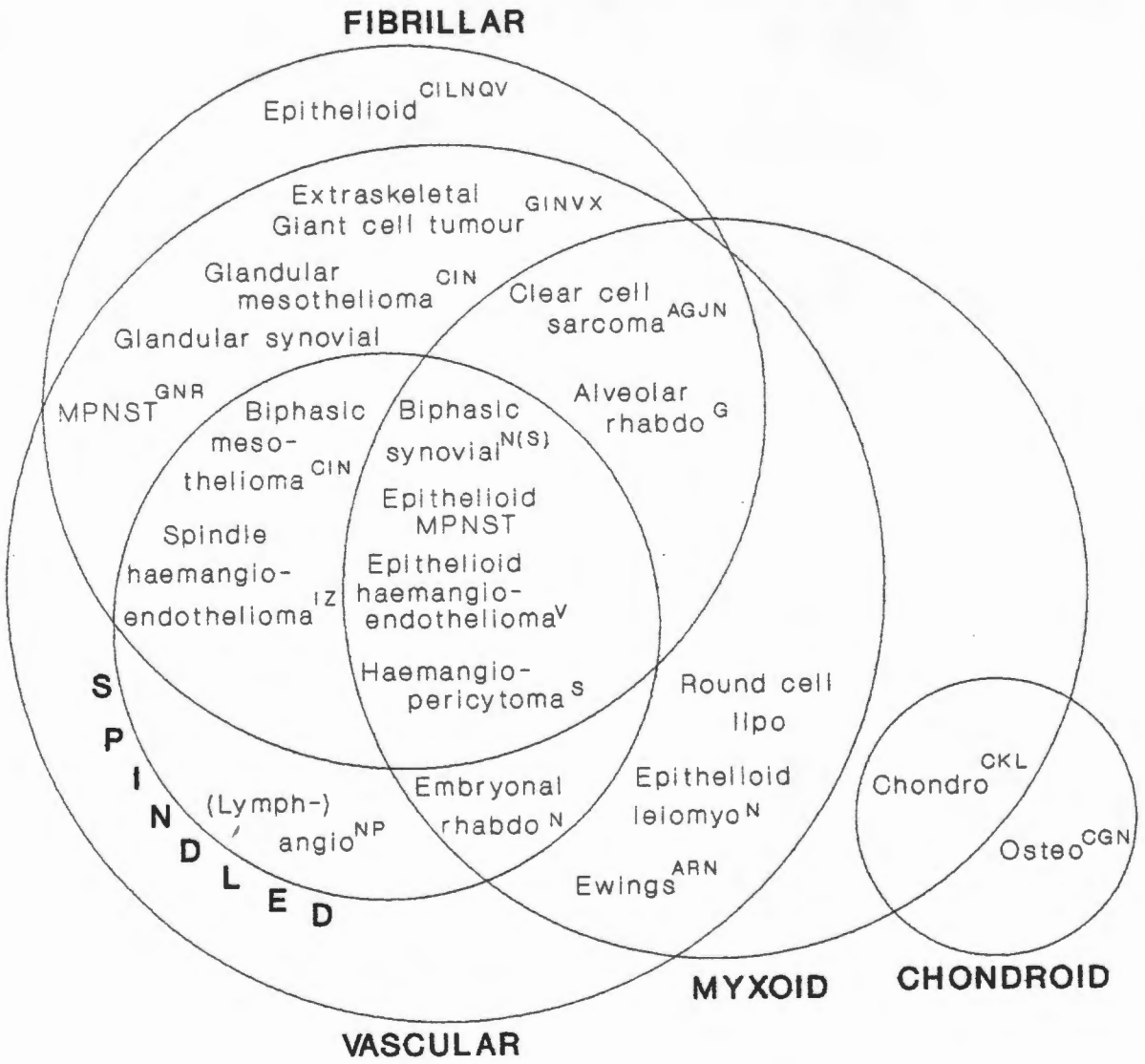
Spindled. Fibrillar areas possible



C Calcification
D Inclusions
E Epithelioid cells
G Giant cells
I Inflammatory cells
N Necrosis
S 'Staghorn' vessels
T 'Triton' tumour if rhabdomyosarcoma admixed
X Xanthoma cells
Z Phleboliths/thrombi

Fig 5.4 **Epithelioid Pattern**

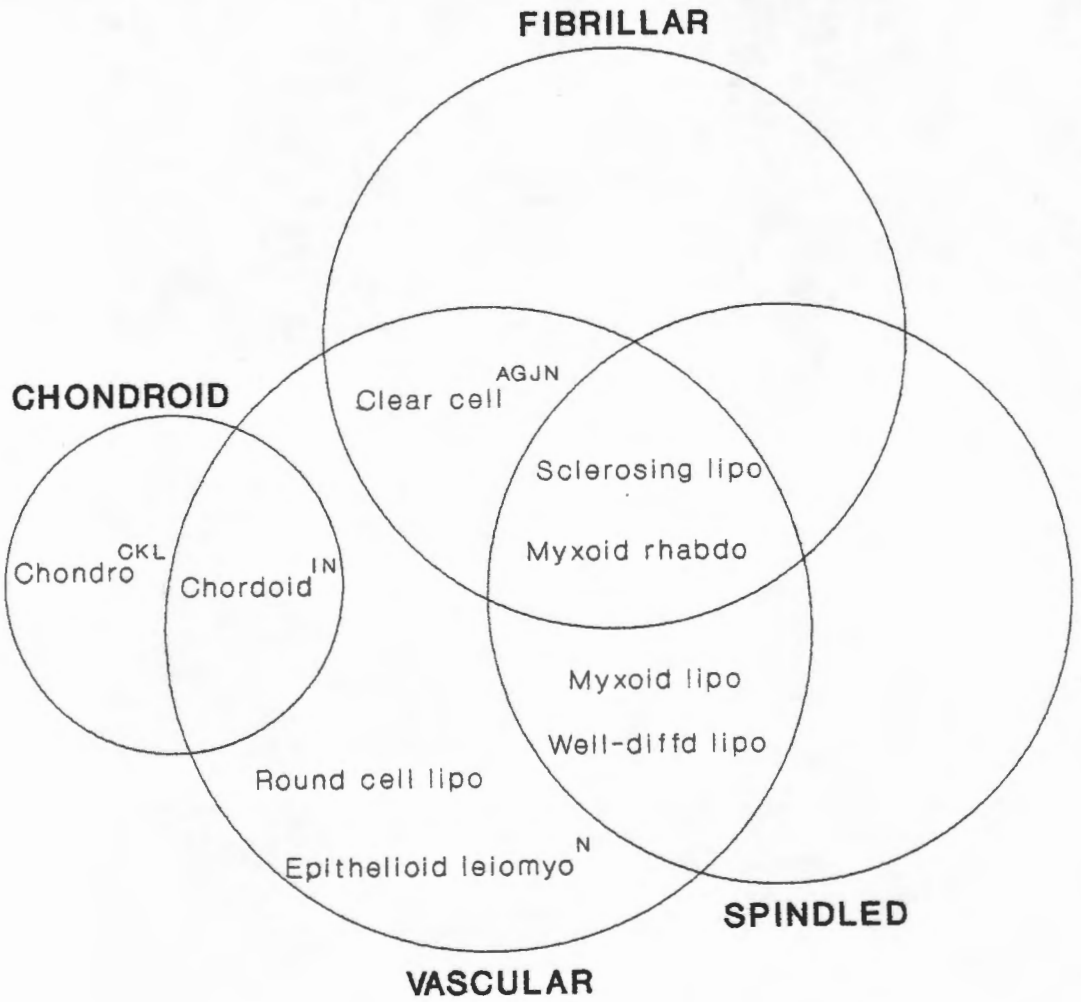
Epithelioid cells



A 'Nested'arrangement
C Calcification
G Giant cells
I Inflammatory cells
J Intracellular melanin
K 'Mesenchymal' if spindled areas
L Multilobular pattern
N Necrosis
P Papillae
Q Spindled areas
R Rosettes
S 'Staghorn' vessels
V Sclerosed areas
X Xanthoma cells
Z Phleboliths/thrombi

Fig 5.5 **Lacy Pattern**

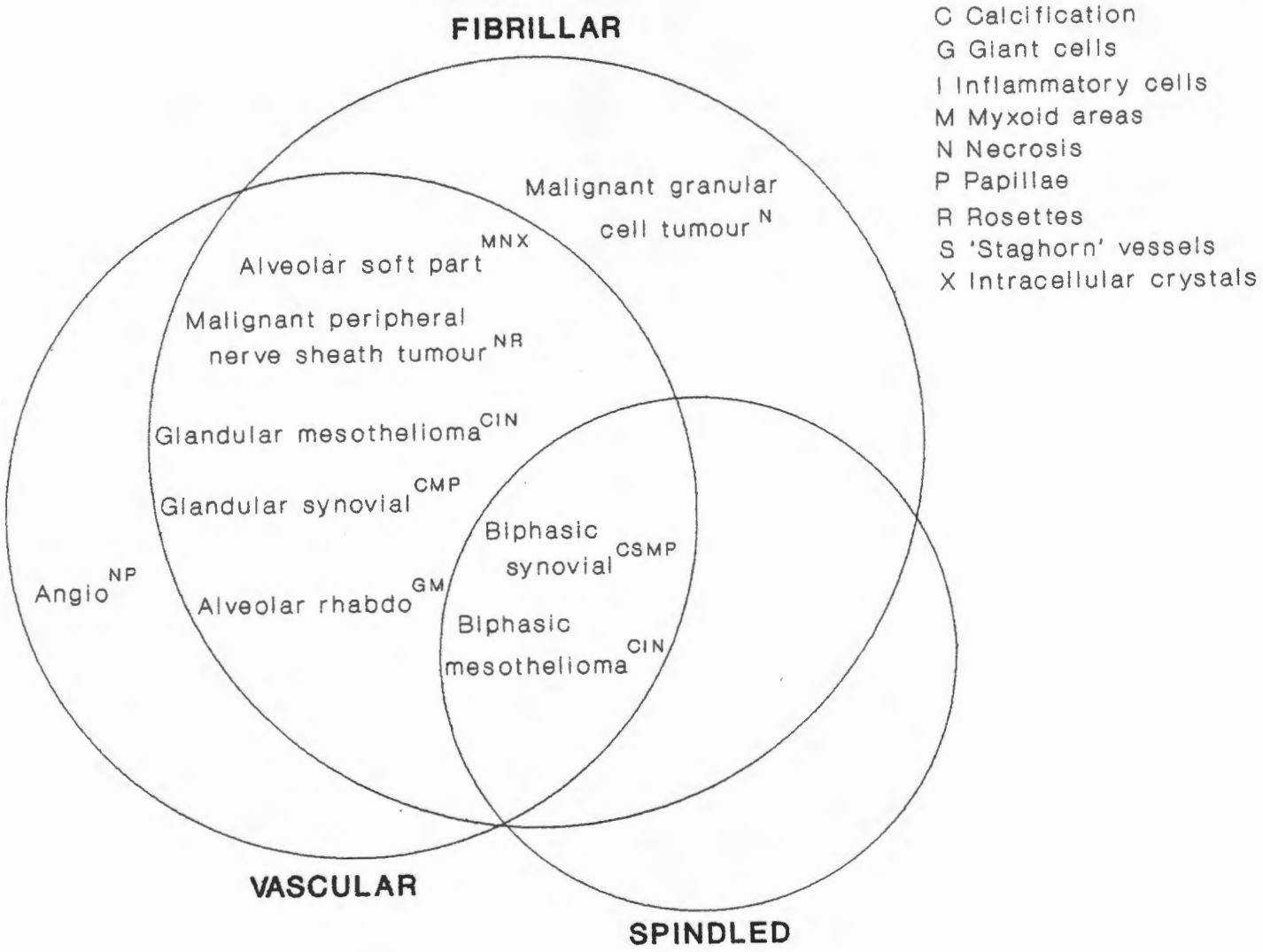
Myxoid areas, epithelioid cells
(except sclerosing liposarcoma)



A 'Nested' arrangement
C Calcification
G Giant cells
I Inflammatory cells
J Intracellular melanin
K 'Mesenchymal' if spindled areas
N Necrosis
L Lobulated pattern

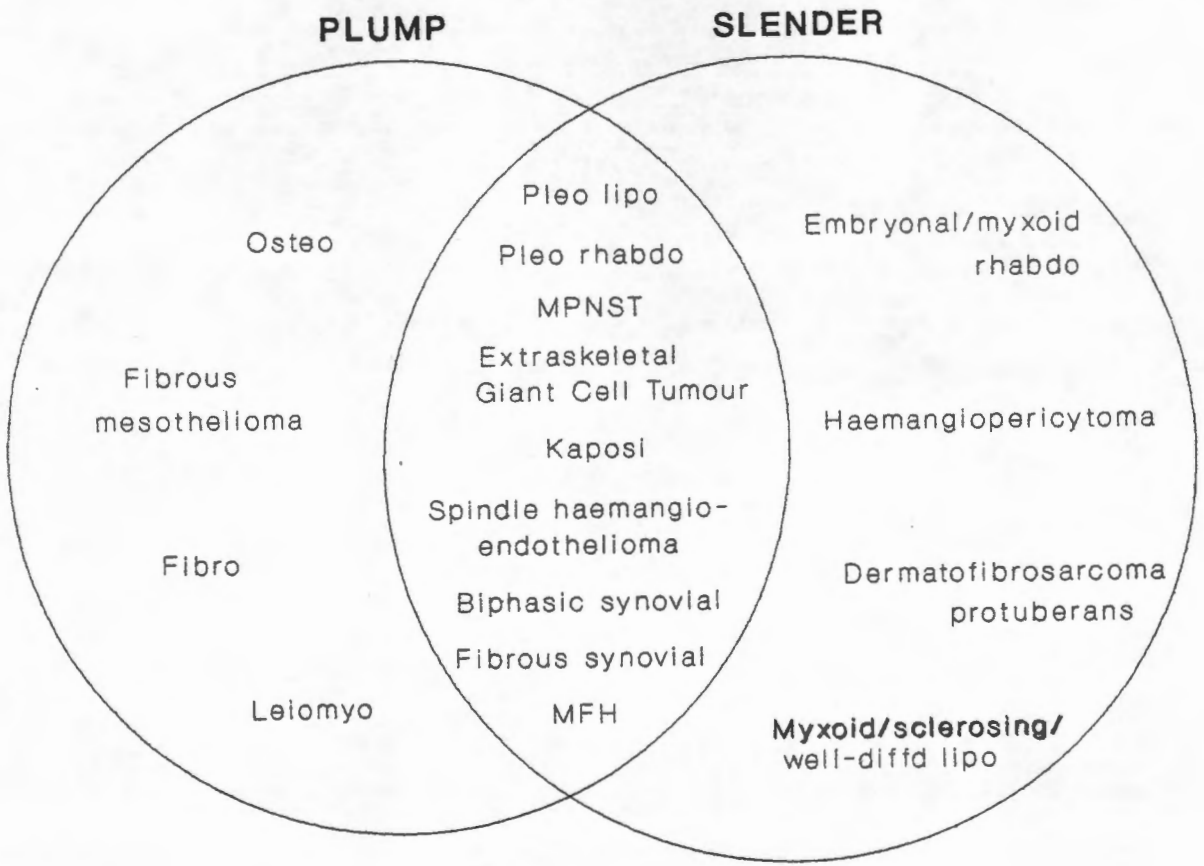
Fig 5.6 **Alveolar/'Glandular' Pattern**

Epithelioid cells



C Calcification
G Giant cells
I Inflammatory cells
M Myxoid areas
N Necrosis
P Papillae
R Rosettes
S 'Staghorn' vessels
X Intracellular crystals

Fig 6 **Spindle Cell Morphology**



INDEX TO PLATES

(The Plates Illustrate Morphological Terms Employed in Figures 5. Historical Material as Re-evaluated Has Been Used Wherever Possible).

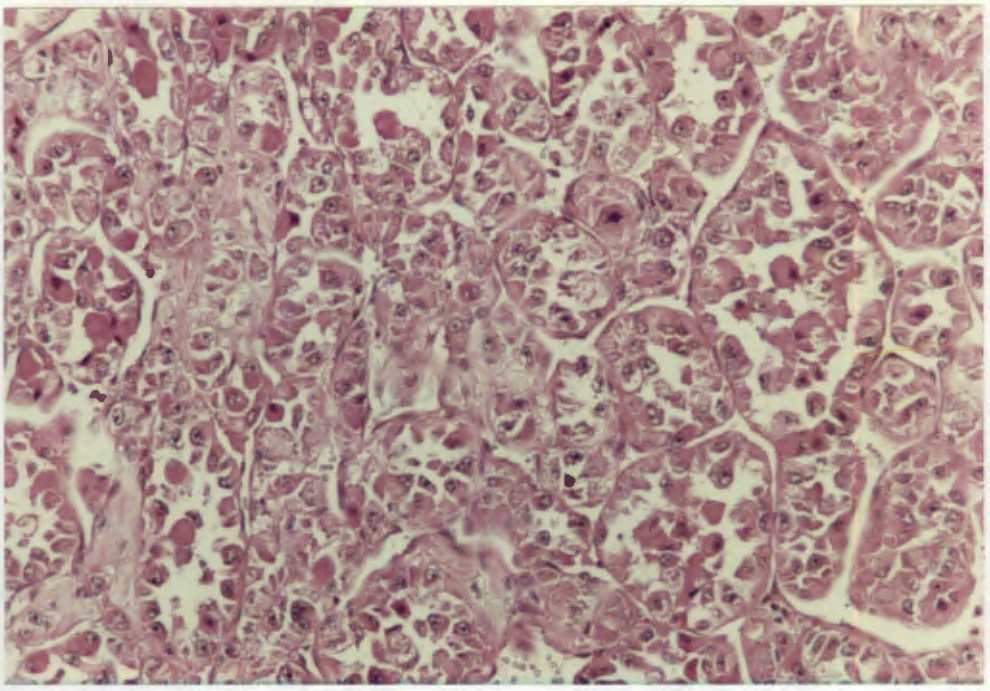


PLATE 1 ALVEOLAR

(Alveolar Soft Part Sarcoma)

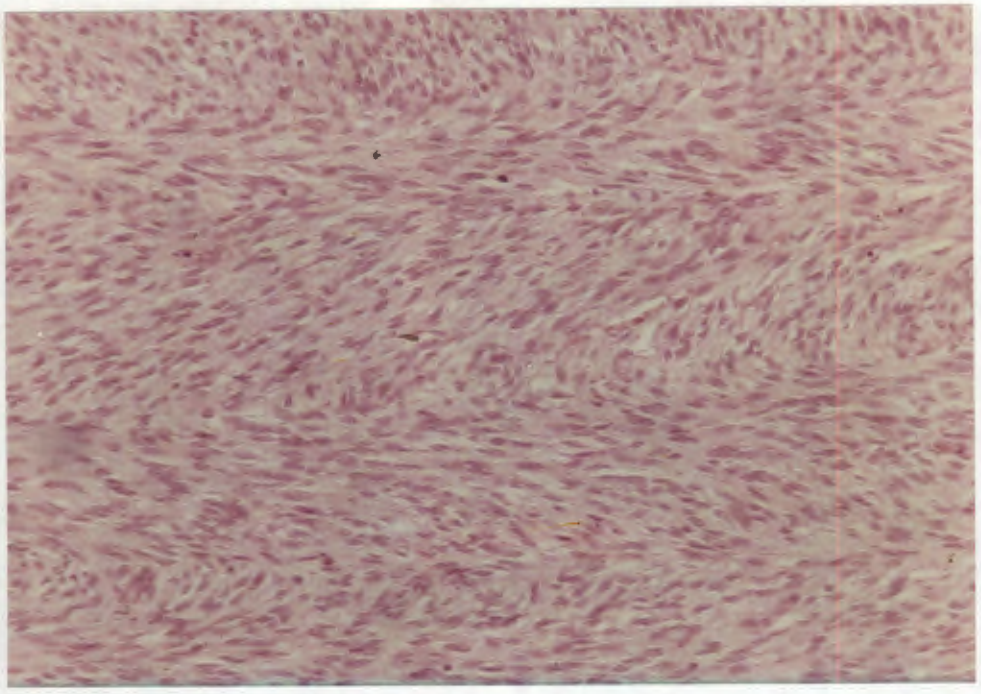


PLATE 2 ARRANGED - "HERRINGBONE"

(Fibrosarcoma)

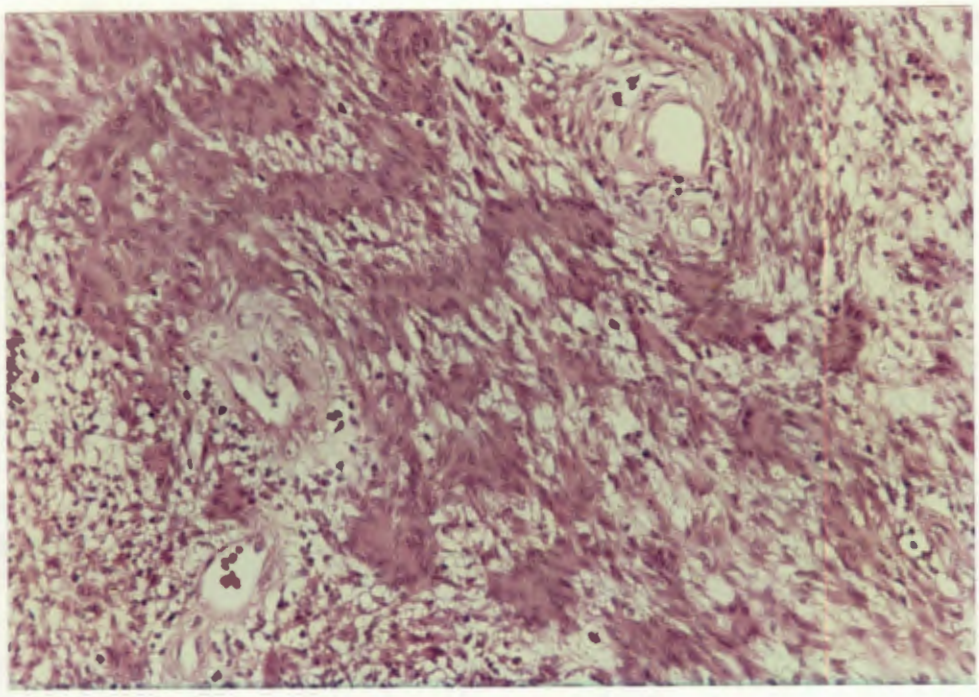


PLATE 3 ARRANGED - PALISADED

(Malignant Peripheral Nerve Sheath Tumour)

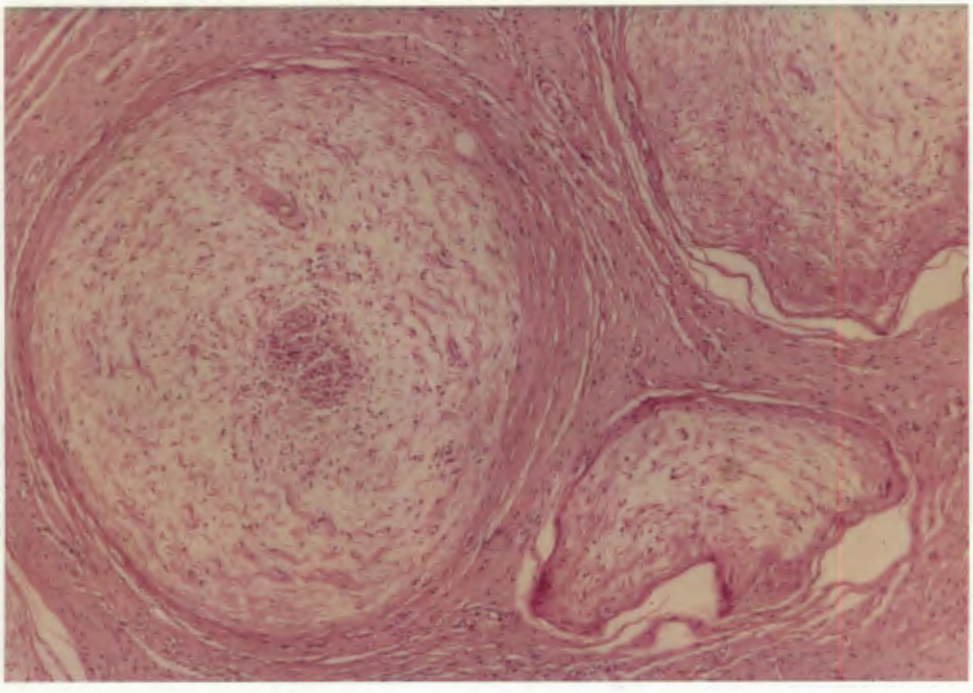


PLATE 4 ARRANGED - PLEXIFORM

(Malignant Peripheral Nerve Sheath Tumour)

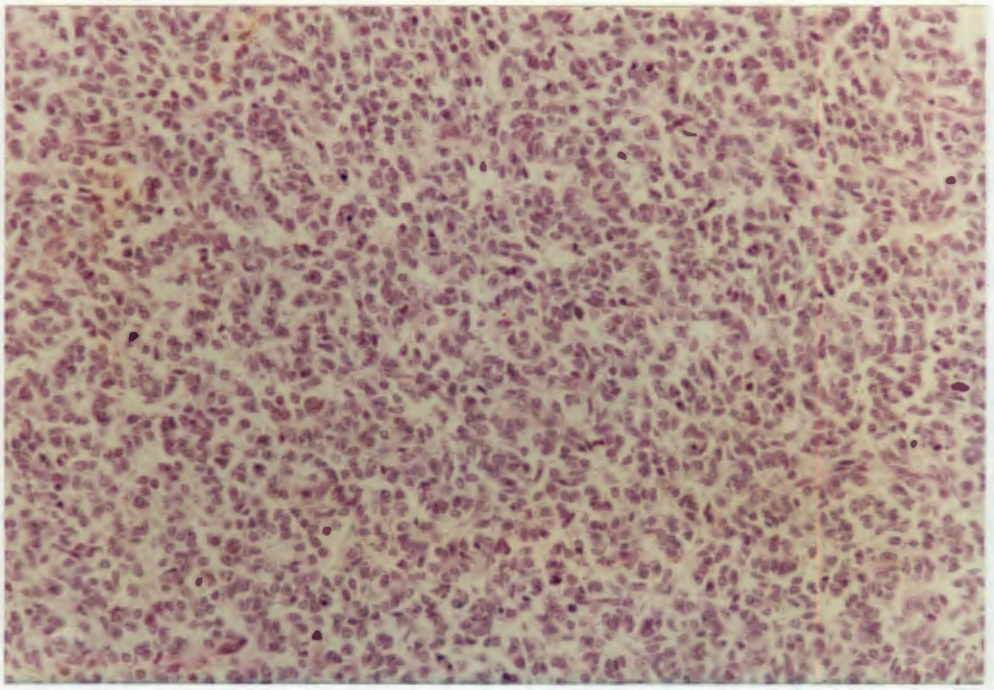


PLATE 5 ARRANGED - ROSETTES

(Ewing's Sarcoma)

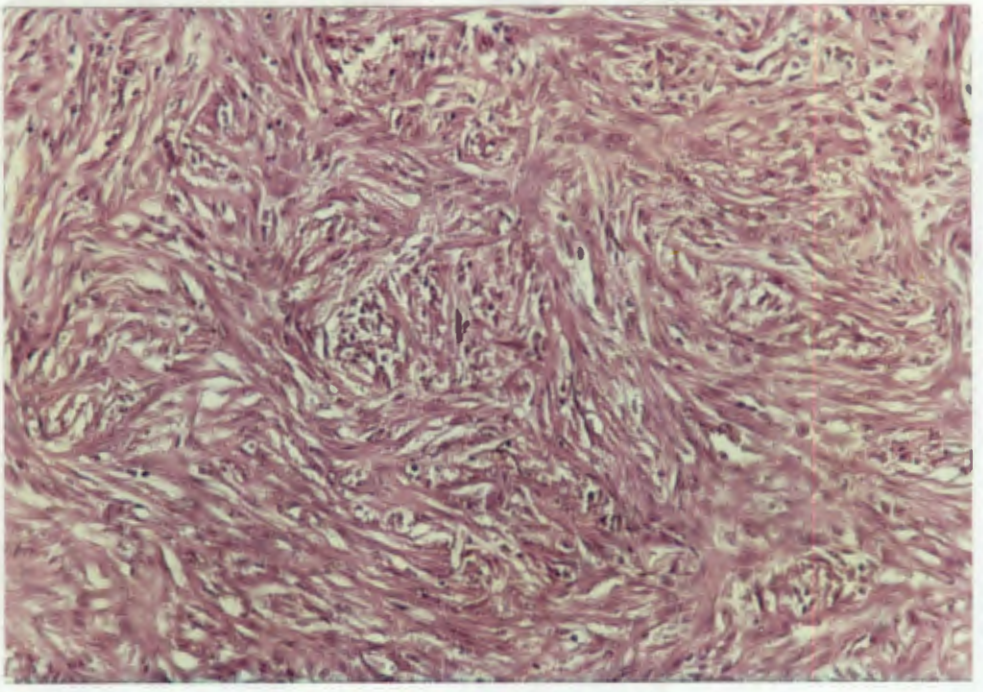


PLATE 6 ARRANGED - STORIFORM

(Dermatofibrosarcoma Protuberans)

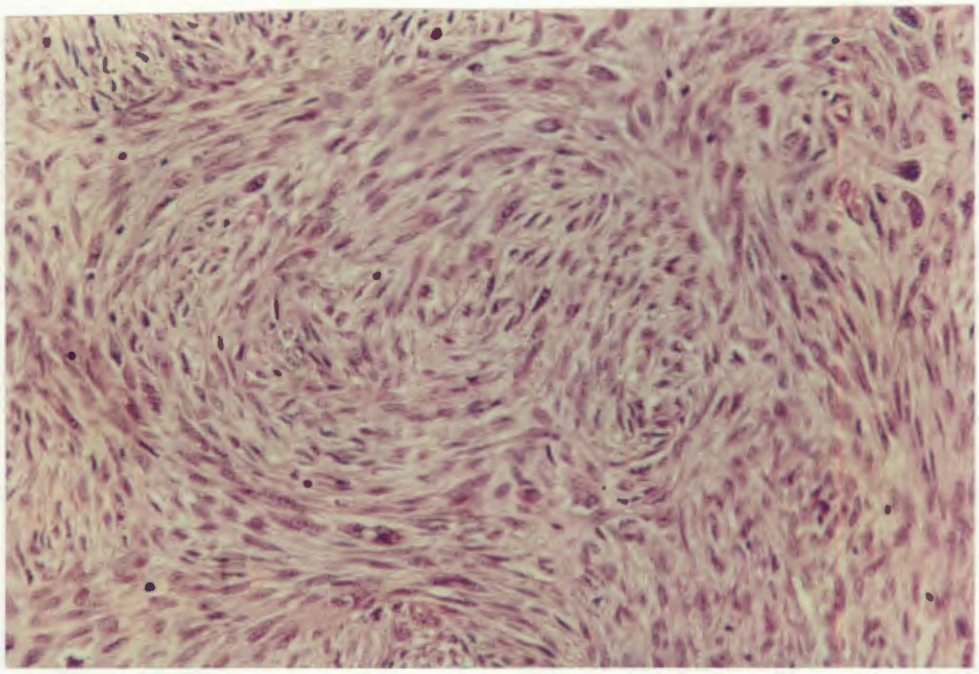


PLATE 7 ARRANGED - WHORLED

(Malignant Peripheral Nerve Sheath Tumour)

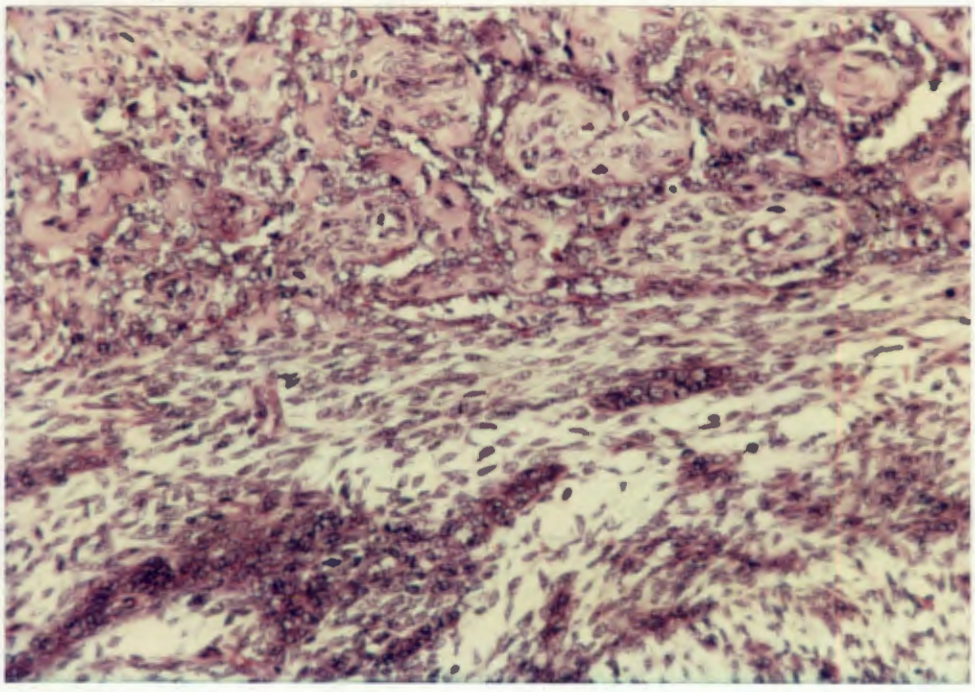


PLATE 8 BIPHASIC

(Synovial Sarcoma)

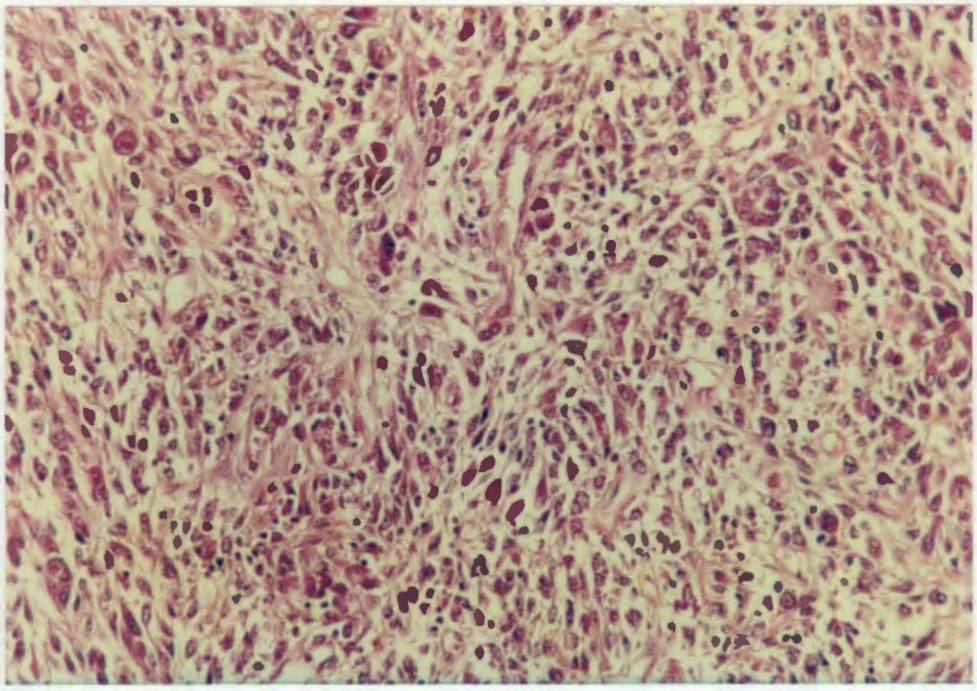


PLATE 9 DISARRANGED

(Malignant Peripheral Nerve Sheath Tumour)

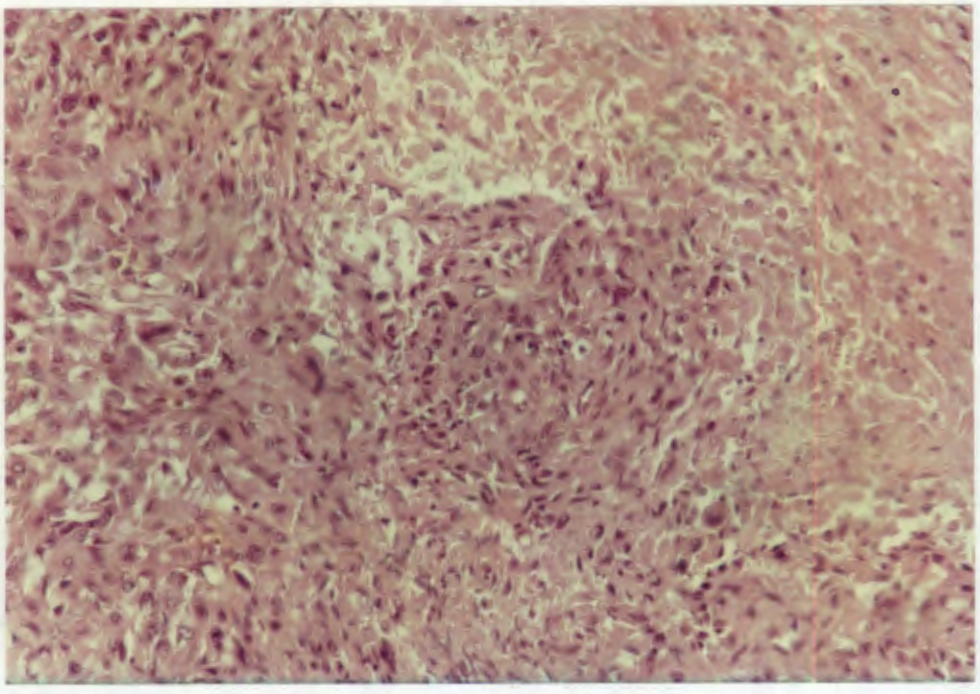


PLATE 10 EPITHELIOID

(Epithelioid Sarcoma)

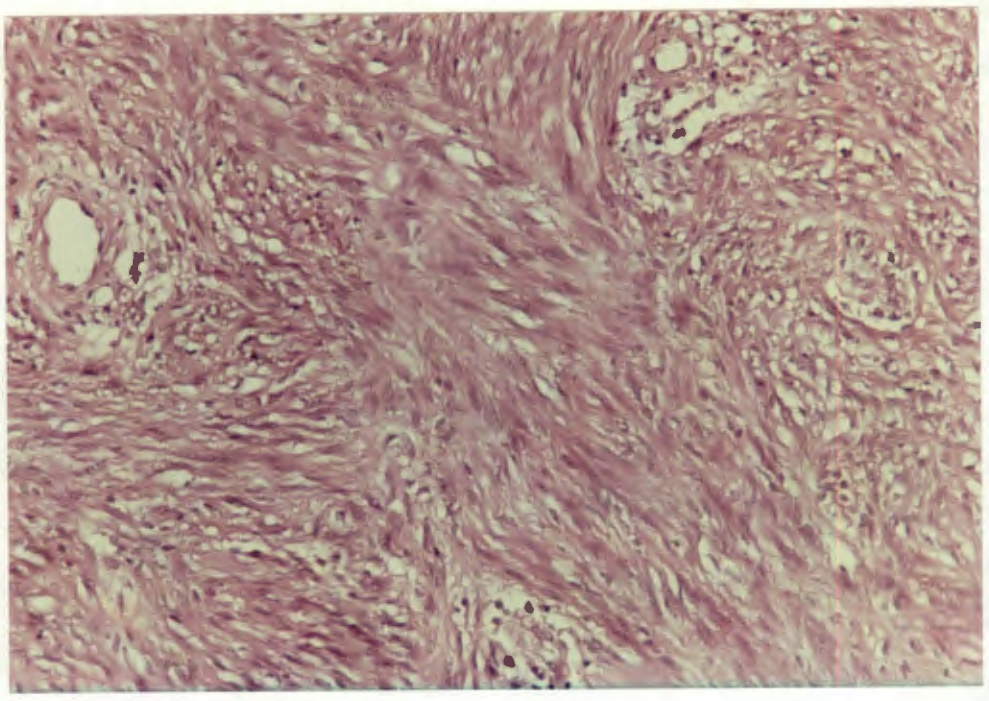


PLATE 11 FIBRILLAR

(Malignant Peripheral Nerve Sheath Tumour)

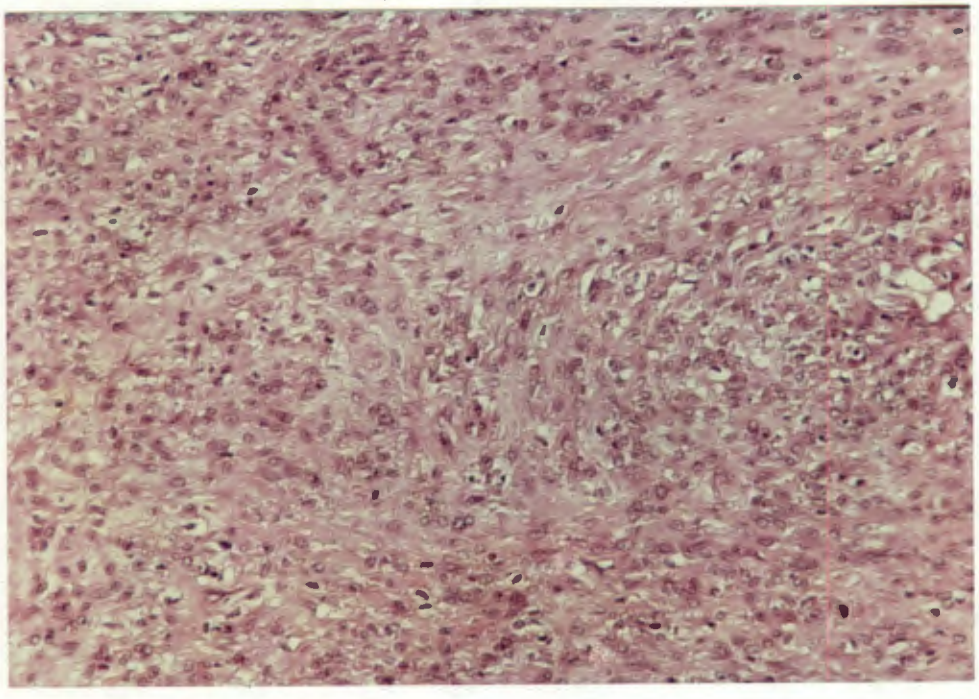


PLATE 12 HYALINE/SCLEROSED

(Synovial Sarcoma)

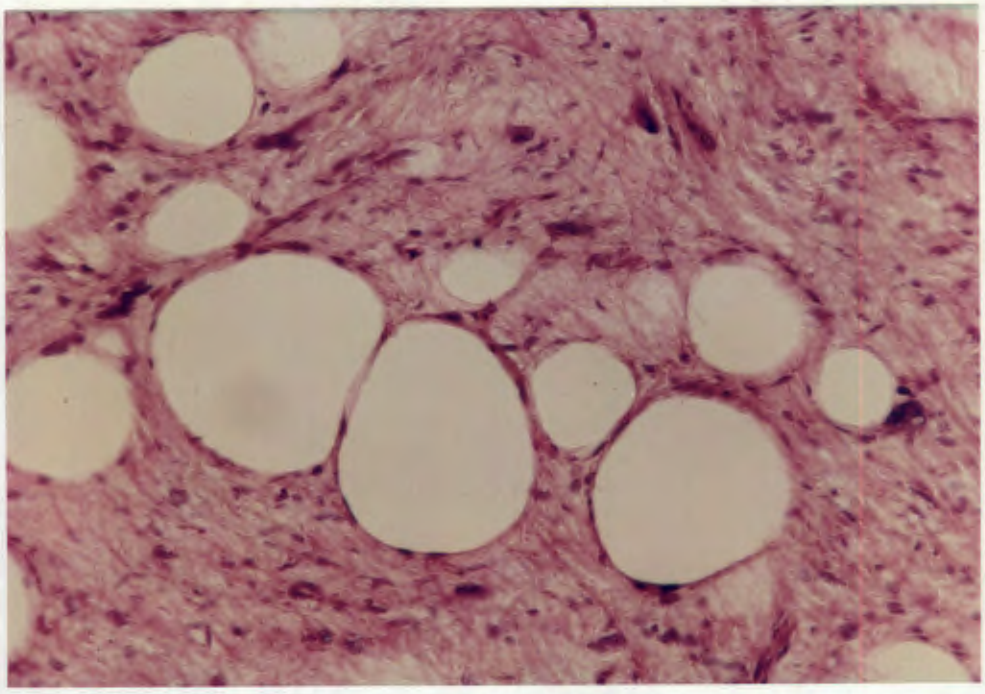


PLATE 13 LACY

(Liposarcoma)

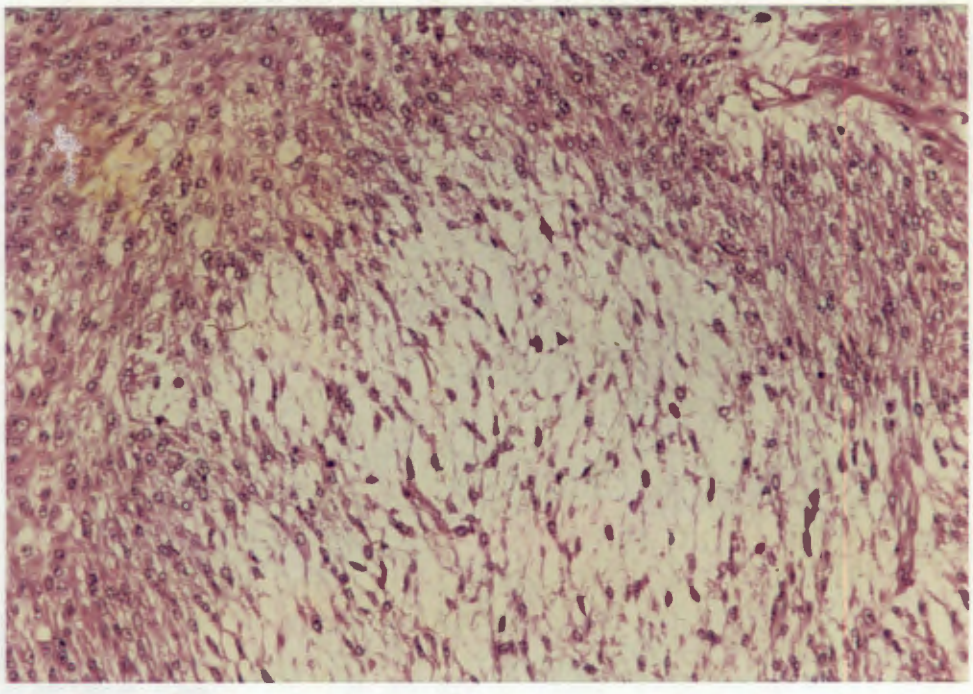


PLATE 14 MYXOID

(Spindle Cell Sarcoma NOS)

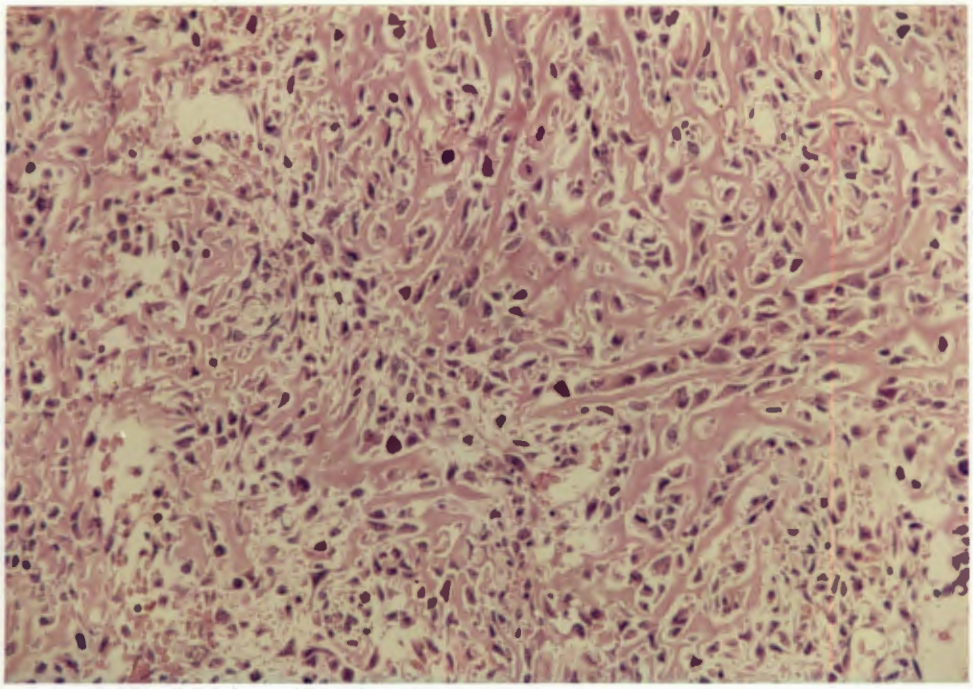


PLATE 15 OSTEOID

(Extraskeletal Osteosarcoma)

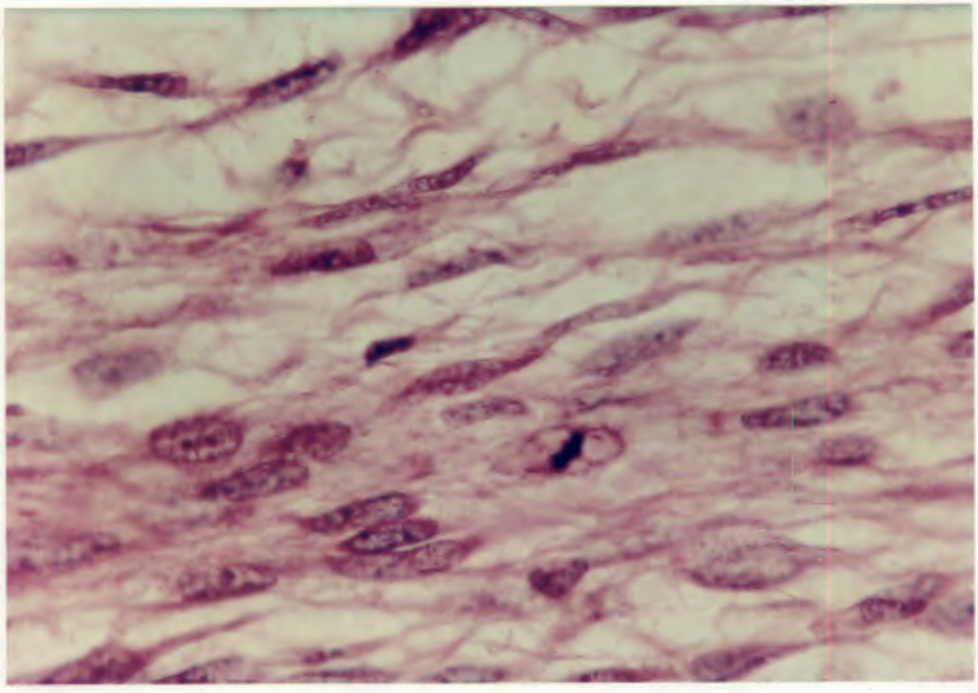


PLATE 16 SPINDLE CELLS - PLUMP & SLENDER

(Malignant Peripheral Nerve Sheath Tumour)

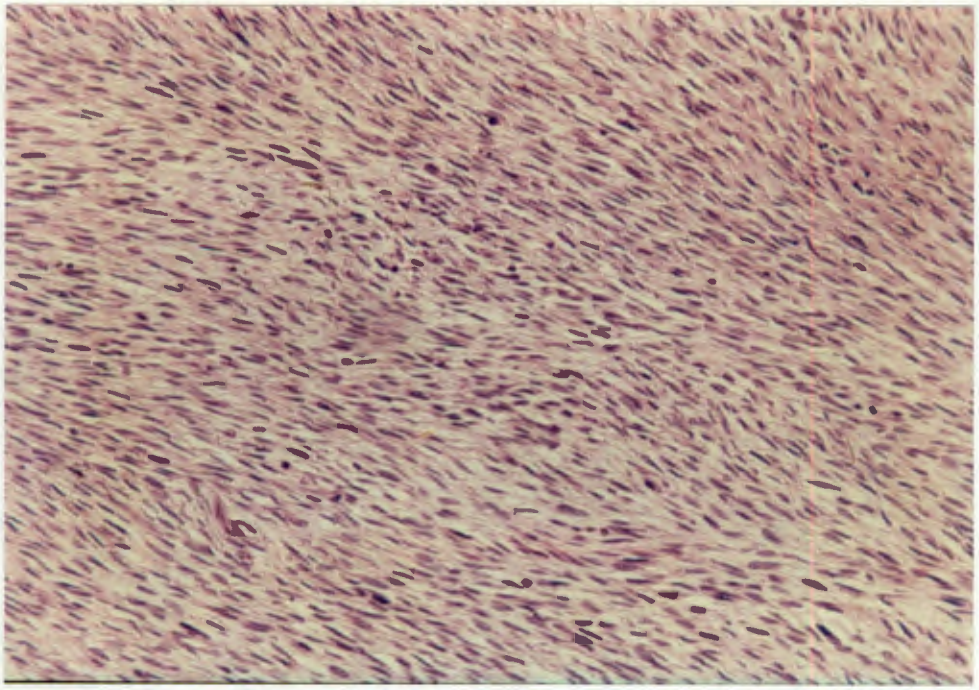


PLATE 17 SWEEPING

(Malignant Peripheral Nerve Sheath Tumour)

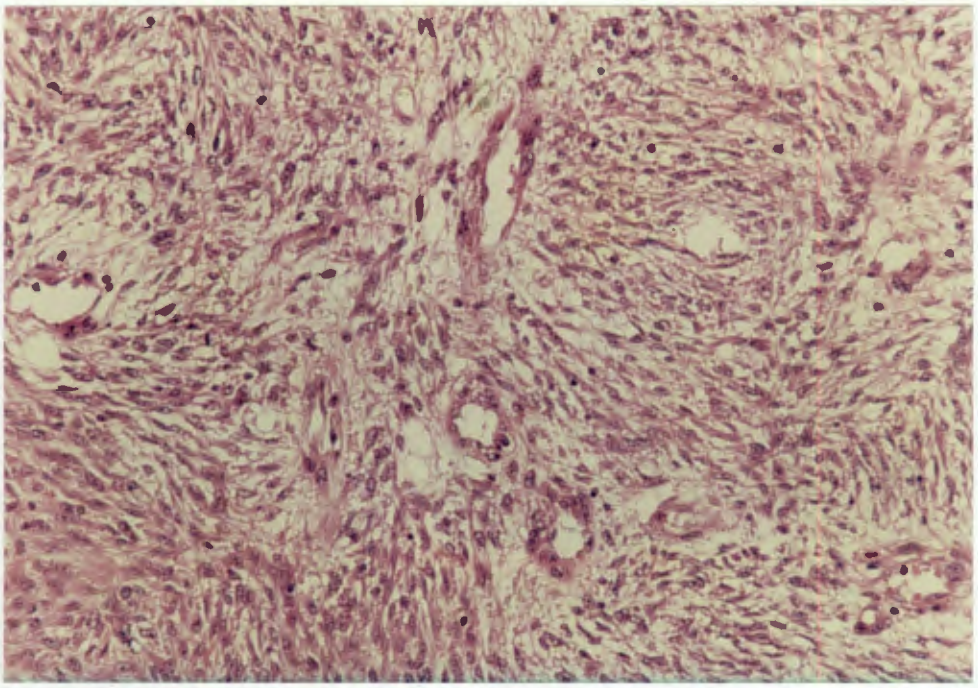


PLATE 18 VASCULAR

(Spindle Cell Sarcoma NOS)

CHAPTER 7
CONCLUSION

A reinvestigation, almost entirely by morphology as determined by light microscopy, but with IHC supplementation where indicated and possible, has been undertaken into a modest historical series of sarcomas of approximately thirty year vintage. Clinico-pathological correlations were expressly not sought. A supplementary aspect of the survey has been the presentation of subsequent statistics of sarcoma diagnosis within a large Southern African pathological practice which has had the privilege to act as a referral centre, and whose experience, for that reason, has been wide though possibly not typical. A comparison of the findings in this context with those of centres elsewhere in the world has shown some minor idiosyncrasies, but an overall resemblance. The broadest conclusion to be drawn from the exercise is that the difficulties encountered in this field are principally nosological, i.e. related to flux of diagnostic criteria and to the burgeoning description of new entities (which, it may be observed, appears to be undergoing a current growth phase). It should also be remarked that, without a demonstration of idiosyncratic clinical behaviour, the description of a new entity is to a large extent sterile. If two sarcomas have the same prognosis and response to therapy, a nosological separation because of subtle morphological differences is academic, and there is a distinct impression that this may be

the case with many currently-described exotica. Yet this is not entirely true; *post hoc propter hoc*, the recognition of clinically deviant behaviour and response to therapy are probably not always the first things to be noted, but sometimes the last.

This study has generated a recommendation for future reporting, namely that:

not only the macroscopic description of the specimen but the number of blocks taken and the procedures to which they are subjected be scrupulously recorded. The blocks should be individually identified by labelling at the time they are taken from the bulk specimen, and, if the specimen is macroscopically inhomogeneous, the labels incorporated into the macroscopic description.

the microscopic description of diagnostic features not readily discerned in the majority of blocks be similarly recorded and at least one representative block be identified in each case.

the report should terminate with an explicit list, in words, of at least the topographical and morphological SNOMed codes under which it is to be recorded. These may lie anywhere in the spectrum between the specific or the non-specific, but will represent in every case no less than the diagnostic limit to which the pathologist is prepared to commit himself. (Very similar proposals, among others, have recently been made independently by the Association of Directors of Anatomic and Surgical Pathology).[150]

Finally, arising out of this study, a practical scheme for the preliminary categorisation of a sarcomatous lesion is presented, which it is hoped winnows key features, enabling the pathologist whose everyday experience does not include these fascinating neoplasms to arrive more speedily at a provisional diagnosis which provides a point of entry to second-order reading.

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APPENDIX

CASES INCORPORATED IN THIS STUDY AS ORIGINALLY DIAGNOSED

A question mark indicates a diagnosis thought probable.
The order is that of increasing SNOMed morphology code

SARCOMA NOS (S = specifically reported as Spindled)

1960	4822	5338	8897						
1961	2538	3327	3663?	3589S	3784	4409	4840	5490	6151 (vascular) 9463S?
1962	1001	2570	3489	3887?	5679S	6043	6293	6721S	
1963	2482	5088	5698	6347S	7025?				
1964	1656S	3142	3750	7654	8433?	9633			
1971	2694	3631	3768	3815	4490?	6923S	8473	9068S	12632S
1972	356	2912S	3451S?	11662					
1973	725?	4649	4659S	5284S	5789				
1974	11758								
1975	525	2748	12535	13591					
1976	999?	2897?	3936	5438	5576	9392S	13275?	13318S?	
1977	8608S	9789S	10267	15136					
1978	5265	6058	12447S	12968					
1980	4432?								
1981	4889	12196S	15015S						
1982	1952?	7393	10137S	11915	16097S?				
1986	2027	3491S	4412	5511?	12945				
1987	8845?	9076?	10485	13095	16150	16813			
1988	2236	2774?	5376?	5955S	7337?	8951	10239	13723	
1989	7869	10083?							
1990	8613	10252S	11146S	4492					

EPITHELIOID SARCOMA

1960-4	none	
1970-4	none	
1975	10759	
1976	4950	9248
1977-8/		
1980-1	none	
1982	8639	
1986-7	none	
1988	10439	
1989-90	none	

FIBROSARCOMA

1960	6882?	7734	8576	
1961	2775	5468	7749	9054
1962	8084			
1963	1722	2343	7560	
1964	none			

(Fibrosarcoma contd)

1971	5418	5945?								
1972	6081?	8154?	9230?	11260?						
1973	61?	6325	8696	10272						
1974	10581?	13359								
1975	12821									
1976	none									
1977	3636	14312								
1978	420	4800?	10767	11317?						
1980	4169?	12607?								
1981	927									
1982	none									
1986-9	none									
1990	2976									

MALIGNANT FIBROUS HISTIOCYTOMA (H)
MALIGNANT FIBROXANTHOMA (X)

1960-4 not applicable

1971-2	none									
1973	2084X?	5847X								
1974	4573X	8428X	11447X	13236X						
1975	3956X?	4031X?	11321X?	11804X	12167X					
1976	12267X									
1977	2142X	7386H	11006H	12502X						
1978	1445H	7317H?								
1980	3500H	3555H	12744H							
1981	1100X	8781H	15249H							
1982	3013H	8166H	13595H?	15930H						
1986	1451H	7058H?	8082H?	17336H?						
1987	5350H	9296H?	9424H	9598H	14195H					
1988	7593H?	10456H	13739?	18171H	18819H					
1989	1588H	2483H?	3176H	3898H	4620H	7615H	7929H	8888H	13339H	13444H
1990	729H	730H	2944H	12951H	15496H?					

DERMATOFIBROSARCOMA PROTUBERANS

1960	none					
1961	712	2193	2473			
1962	10067					
1963-4	none					
1971	none					
1972	10304					
1973	65?	110	1780	7088	7328	8943
1974	3061					
1975,6	none					
1977	2192	13188?				
1978	11479	14733				
1980	none					
1981	5414					

(DFP contd)

1986	1037	5018	5183
1987	none		
1988	2934	17069	
1989	1004	4945	11707
1990	651	10733	14142

MYXOSARCOMA

1960,1	none
1962	8882?
1963	none
1964	5786
1971-8/	
1980-1	none
1986-90	none

LIPOSARCOMA (M = myxoid, P = pleomorphic, R = round-cell, S = sclerosing, W = well differentiated, # = mixed)

1960	none										
1961	5694?										
1962	3470	5921	5997								
1963	none										
1964	[3828, vide 6567, case unassessable]						6869 ?				
1971	3075M	4395W	10842W								
1972	927W	4197M	7698P	9125P							
1973	1056W	3349#	8645M	9053 W							
1974	2819W	3267M	3341M	8174P	9426WS	13360					
1975	3157WS	3562M	3996W	4664M	6698W	9252R	12752W	13057W	13066M		
1976	1285M	1459M	2076W	2383W	3563M	5456M	6822	10095W	11378M	13100W	13291P
1977	846W	1271W	2950	5647M	6514	10176W					
1978	1870M	4347M?	5284M								
1980	2781PS	3557	4245#	8988P							
1981	6026M	8644S?	9416M								
1982	none										
1986	3793M	12278P									
1987	4301M	4810W	15331P								
1988	4750?	7558M									
1989-90	none										

LEIOMYOSARCOMA

1960-1	none	
1962	993	
1963	5468	
1964	5581	8906

(Leiomyosarcoma contd)

1971	4946			
1972	none			
1973	3716 ?			
1974-5	none			
1976	2948			
1977	1573			
1978/				
1980	none			
1981	1557	4982	6506	
1982	8963			
1986	13371	14104		
1987	5960?	9420?		
1988	1820	3343	4867	12494
1989	438			
1990	none			

RHABDOMYOSARCOMA (A = alveolar, B = botryoid, E = embryonal, P = pleomorphic)

1960	4132				
1961	6213?				
1962	9534B				
1963	8535				
1964	none				
1971	2532A	2761B	5442B?	10207P	
1972	11048E				
1973	4402B	5826?	8152E	8328P	12580P
1974	1680	9141E			
1975	8198P	10129	11703E	12970P	
1976	1354E	2226E			
1977	13293?				
1978	1600E	3510	10366E		
1980	1010A	11325?			
1981	none				
1982	4156P	7739	11680B		
1986	4996E				
1987	4962A	8555?	10069A	17412EP	
1988	5326	15579E			
1989	9602	16210			
1990	2089E	2597E	8363P		

MALIGNANT MESENCHYMOMA

1960-3	none
1964	2808?
1971	none
1972	9253?
1973-8/	
1980-2	none

(Malignant Mesenchymoma contd)

1986 none
1987 70?
1988-90 none

SYNOVIAL SARCOMA (B = biphasic, M = monophasic)

1960 5892
1961-2 none
1963 5773
1964 none

1971 12136?
1972 4702B
1973 8691 10169B
1974 4880B 6740B
1975 12298B?
1976 6976B 10398?
1977 6889M
1978 10486B 11002B?
1980 8903M 15983M
1981 16398B
1982 9227M? 12187M?

1986 4883M 6776M 7552B 18510B
1987 1011
1988 9899M
1989 71? 13099B
1990 6384 6886M 10696B 14207?

CLEAR CELL SARCOMA

1960-4 not applicable

1971 4778
1972-6 none
1977 6817? 9478
1978 none
1980 6448? 8631 9935?
1981-2 none

1986 8845
1987 none
1988 16818?
1989-90 none

ANGIOSARCOMA

1960-4 none

1971-4 none
1975 7653?
1976-8/

(Angiosarcoma contd)

1980 none
1981 14287
1982 9337 14699

1986 none
1987 300 10328? 11648
1988 16607 (occult primary)
1989-90 none

MALIGNANT HAEMANGIOENDOTHELIOMA

1960-4 none

1971-8/
1980 none
1981 7666?
1982 none

1986-90 none

KAPOSI'S SARCOMA

1960-2 none
1963 284? 1887?
1964 8172

1971 5099
1972 8163 9397 9699 11517
1973 6802 10254
1974 none
1975 10023 10653 12390?
1976 6388 9956 10137 10206 13722
1977 1184?
1978 2641 7179 9883 13693
1980 842 6753? 16227
1981 11235 14472?
1982 1009? 1299 7437 15146

1986 11314 13762
1987 1323 2846 11035
1988 2982 6289 6763 7265 13714 14209 16914?
1989 7094 11996
1990 4223 6599 6825 12002 15382 15654

MALIGNANT HAEMANGIOPERICYTOMA

1960 none
1961 4044
1962 1696
1963-4 none

(Malignant haemangiopericytoma contd)

1971-8 none
1980 3556
1981 none
1982 2309

1986 none
1987 3103
1988-90 none

EXTRASKELETAL OSTEOSARCOMA

1960-4 none

1971-8/
1980-2 none

1986-7 none
1988 2388? 7594
1989-90 none

EXTRASKELETAL CHONDROSARCOMA

1960-4 none

1971 3777
1972-8/
1980-2 none

1986 14305
1987-90 none

EXTRASKELETAL MALIGNANT GIANT CELL TUMOUR

1960-4 none

1971-3 none
1974 715
1975-7 none
1978 3440 8678
1980-2 none

1986-90 none

EXTRASKELETAL EWING'S SARCOMA

1960-4 none

1971-8/
1980-2 none

(Extraskeletal Ewing's Sarcoma contd)

1986-7	none			
1988	11827	8840		
1989	9058	13280		
1990	none			

MALIGNANT PERIPHERAL NERVE SHEATH TUMOUR

(N = neurofibrosarcoma, S = Malignant Schwannoma,
T = Triton (i.e. rhabdomyoblastic differentiation.)

1960	13284N?			
1961	89?	3022?		
1962	292S			
1963	18178N?	5412N		
1964	none			
1971	7793N	11045N?		
1972	6168N			
1973	1492N	3789S?	9170N?	10508?
1974	4504N	9636?	11196S?	
1975	4385S			
1976	426N	675N		
1977	none			
1978	3439N	5870S		
1980	11083S			
1981	none			
1982	609	11196		
1986	715S	8887N	18014	
1987	9808			
1988	554N	1286T	11038N?	
1989	12516N	12930S		
1990	4661S	5070N		

MALIGNANT GRANULAR CELL TUMOUR

1960-4	none
1971-8/	
1980-2	none
1986	none
1987	3754
1988-90	none

ALVEOLAR SOFT PART SARCOMA

1960-1	none	
1962	953	8072
1963-4	none	
1971-3	none	
1974	1524	
1975-6	none	
1977	1219	
1978	none	
1980	9283	
1981-2	none	
1986-90	none	